VOL. 50 NOVEMBER, 1955 No. 5

AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION FOR THE STUDY OF THE CIRCULATION

Contents on Inside Cover

American Heart Journal

CONTENTS FOR NOVEMBER, 1955

Original Communications

Clinical Reports

Review

Book Review

Announcements

Vol. 50, No. 5, November, 1955, American Heart Journal is published monthly, by The C. V. Mosby Company, 3207 Washington Avenue, St. Louis 3, Missouri, entered as second class matter January 23, 1917 at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription Price: United States, and its Possessions, per year $12.00; Canada $13.00; Foreign $13.50. Printed in the U. S. A.

American Heart Journal

Vol. 50 NOVEMBER, 1955 No. 5

Original Communications

THE OCCURRENCE AND POSSIBLE SIGNIFICANCE OF GENERALIZED VASCULAR DISEASE IN IDIOPATHIC CARDIAC HYPERTROPHY

George R. DeMuth, M.D., and Benjamin H. Landing, M.D.

Cincinnati, Ohio

THE observation of the occurrence of widespread vascular lesions in an infant with idiopathic cardiac hypertrophy, and a recent report[1] of similar lesions in a patient with hypertension and striking cardiomegaly have prompted an investigation of the vascular systems of other cases of idiopathic cardiac hypertrophy. A control series of children with normal hearts and a series of children with cardiomegaly due to endocardial sclerosis were also studied. The results are presented after a brief description of the clinical history and pathologic findings of the patient referred to here.

CASE REPORT

G.J. was a 2½-month-old white male who was born after normal pregnancy, labor, and delivery. The family history was of note only in that a male first cousin died as an infant of unknown causes. The patient was well until the age of 2 weeks, when an episode of excessive crying was followed by tachypnea, dyspnea, and cyanosis; these symptoms increased in severity over a period of several hours, and the patient was admitted to the hospital. Physical examination showed tachypnea, dyspnea, and cyanosis; the pulse rate was 212 per minute and the respiratory rate 112 per minute. The blood pressure was 120/80 mm. Hg on one occasion and 130/80 on another. The heart was not enlarged to percussion, and there were no murmurs. The liver was palpable 4 cm. below the costal margin. Repeated blood counts were within normal limits. Spinal fluid protein was elevated (48 to 187 mg. per cent). Serum nonprotein nitrogen was normal (33 to 40 mg. per cent); total protein was 4.6 grams per cent. Urinalyses showed persistent

From the Departments of Pathology and Pediatrics of The Children's Hospital, Cincinnati, and the University of Cincinnati College of Medicine.

Received for publication March 10, 1955.

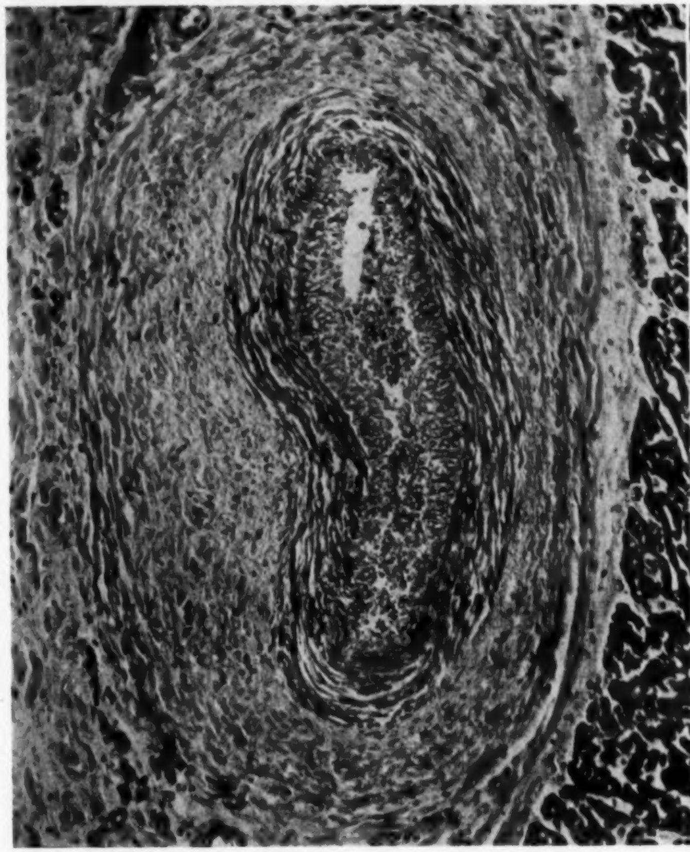


Fig. 1.

Fig. 2.

Fig. 1.—Coronary artery, showing thick adventitia and media, with intimal fibrosis of long axes. Mallory's phosphotungstic acid-hematoxylin stain. (×166; reduced 1/5.)

Fig. 2.—Spermatic artery, showing medial hypertrophy and variable but circumferential intimal fibrous thickening. Hematoxylin-eosin stain. (×166; reduced 1/5.)

albuminuria (trace to four-plus), and occasional red and white cells. Initial electrocardiograms showed sinus tachycardia, right ventricular hypertrophy, and P pulmonale; later, the changes of right ventricular hypertrophy regressed. Initial x-rays showed pulmonary congestion and a normal heart. Later, the lung fields cleared, but the heart shadow enlarged. Skull films and intravenous pyelogram were normal.

The patient improved with oxygen, morphine, and digitoxin, and the liver receded. He was discharged after one month on maintenance oral Digifolin. After one week, another episode of respiratory difficulty, tachycardia (pulse 152), and cyanosis led to readmission to the hospital. An electrocardiogram showed incomplete right bundle branch block, S-T segment depression in Leads V_R, V_{4R}, V_1, and V_3, and T-wave inversion in Leads I, II, V_L, and V_6. Temporary improvement was followed by relapse; addition of mercurial diuretic and oxygen to the therapeutic regimen caused improvement again, and he was discharged at the age of 7½ weeks. At 2½ months, a fourth attack of dyspnea, cyanosis, and tachypnea caused death at home.

Autopsy: The heart was enlarged, with a transverse diameter of 7.5 cm., as compared to a thoracic diameter of 12 cm. It weighed 52 grams (normal weight 23 grams). The valves were not abnormal. The foramen ovale was functionally closed, and the ductus arteriosus was obliterated. There was no endocardial sclerosis, and the myocardium was firm with no areas of scarring. The right ventricular muscle was 0.4 cm. thick and the left 1.2 cm. The coronary arteries were normally distributed and patent. The aorta and its major branches, the great veins, and all blood vessels noted were grossly normal. There were visceral congestion and edema. The lungs showed chronic pneumonitis with focal emphysema and atelectasis. Focal extramedullary erythropoiesis was present in the liver. The testes showed Leydig cell proliferation, similar to that seen in incomplete true precocious puberty. The kidneys showed focal interstitial infiltration by chronic inflammatory cells, but there were no lesions of the lower urinary tract.

The central nervous system, thyroid, pancreas, gastrointestinal tract, adrenals, spleen, thymus, skeletal muscles, and bones were not unusual.

Microscopically, many muscular arteries in a number of organs (listed in Table I) showed mural thickening, predominantly by hypertrophy of the muscular tissue of the media. Some of these vessels also showed foci of intimal fibrosis without lipid deposit (Figs. 1 and 2). The aorta showed diffuse circumferential intimal fibrosis, again without lipid deposit, but the media and adventitia were not unusual (Fig. 3).

OBSERVATIONS

In an effort to assess the significance of the vascular lesions observed in the patient described here, the microscopic sections available from four other children with idiopathic cardiac hypertrophy were reviewed and compared with those of patients of comparable age with normal hearts. Endocardial sclerosis was selected as a "control abnormal condition" because patients with this disease have cardiomegaly and a clinical course much like that seen with idiopathic hypertrophy. Widespread arterial lesions consisting of medial hypertrophy and intimal fibrosis were found in three of the four other patients previously considered to have idiopathic cardiac hypertrophy; the more important clinical and pathological data on the four patients with vascular lesions are listed in Table I.

Measurement of the thickness of the medias of muscular arteries (the type most strikingly affected) was performed on the sections available. The number measured was 107 in the four patients with idiopathic cardiac hypertrophy, 111 in the five patients with endocardial sclerosis, and 111 in the four control patients. Only arteries cut in cross section were measured; when doubt existed, the average diameter of the lumen was used. The thickness of the media of each

TABLE I. CLINICAL AND PATHOLOGICAL FEATURES OF CASES OF IDIOPATHIC CARDIAC HYPERTROPHY WITH DIFFUSE ARTERIAL MEDIAL HYPERTROPHY AND FOCAL ARTERIAL INTIMAL FIBROSIS

CASE NUMBER	1 C53-91	2 C46-57	3 C47-68	4 C45-38
Sex	Male	Female	Male	Male
Color	White	White	White	White
Age at death	2½ months	6½ months	7 months	2½ years
Age at onset symptoms	2 weeks	3 months	5½ months	3 months
Cardiorespiratory attacks	4 episodes	2 episodes	1 episode	1 episode
Proteinuria	Persistent	Persistent	Demonstrated twice	Not determined
Blood pressure	120-130/80	Increased pulse pressure; values not recorded	Not determined	100/40
Heart weight (grams)	52	65	55	145
Normal heart weight* (grams)	23	31	34	56
Sites of arterial lesions†	Heart	Heart	Heart	Heart
	Pancreas	Colon	Testes	Pancreas
	Kidneys	Kidneys	Mesentery	Kidneys
	Testes	Aorta		Aorta
	Mesentery			
	Aorta			

*Normal heart weights are taken from the data of Coppoletta and Wolbach (Am. J. Path. 9:55, 1953).

†Since all organs were not examined microscopically in all cases, the list of sites of arterial lesions can be considered only as indicating the minimal distribution of abnormal vessels.

vessel was measured on four perpendicular radii, and the average thickness determined. Only vessels with lumen diameters between 50 and 250 microns were studied; the lower limit was chosen to avoid confusion with arterioles, and the upper limit was necessitated by lack of a sufficient number of such vessels in the microscopic sections. Vessels from all parts of the body possible, except lungs and brain, were studied; these organs were excluded because of accumulated evidence that their vascular beds are controlled differently from vessels in other parts of the body. In Table II are listed the median values of medial thickness for the vessels measured in the three groups of patients, divided into groups of approximately equal number. The value for "corrected median" was obtained by selecting from all observations in each range of vessel sizes, arranged in order of decreasing magnitude, the value occupying a position proportionate to the ratio of experimental (idiopathic hypertrophy plus endocardial sclerosis) observations to control observations. In Fig. 4, median widths of

medias are plotted on the ordinate against mean lumen diameters on the abscissa, for the three groups of patients. The fourth line shows the corrected median values.

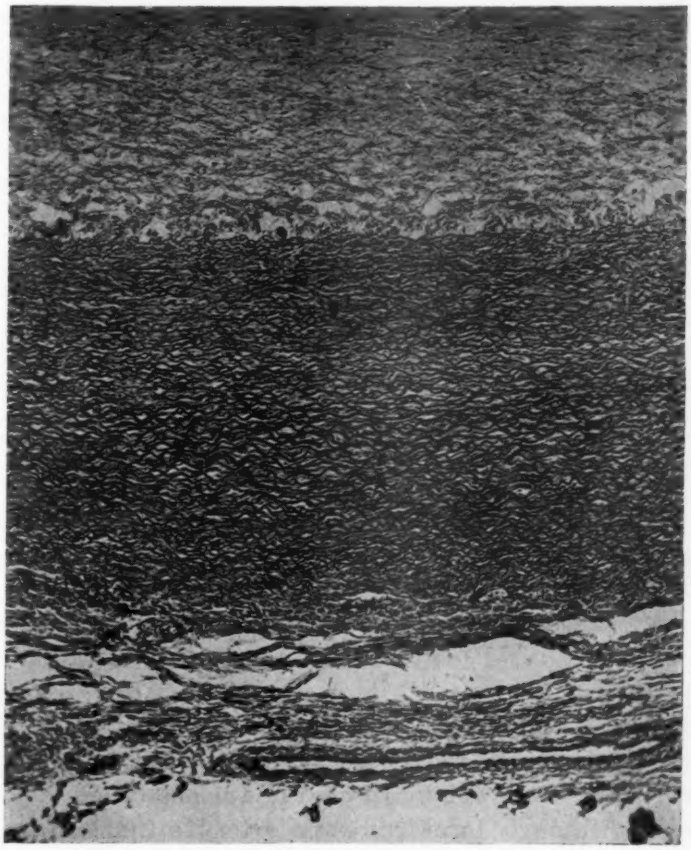


Fig. 3.—Aorta, showing thick layer of intimal fibrosis. Hematoxylin-eosin stain. (×76; reduced 1/5.)

For statistical evaluation, the vessels of each group of patients were divided into those which had thicker and those which had thinner medias than the corrected median values for vessels of corresponding lumen diameter. The figures were used in four-place contingency tables, and the values of Chi-square were determined. For the cases of idiopathic cardiac hypertrophy versus the controls, this value was 61.5, and for the cases of endocardial sclerosis versus the controls it was 33.0. In other words, both the patients with idiopathic cardiac hypertrophy and endocardial sclerosis had muscular arteries with a significant increase in medial thickness, as compared to control patients of the same age. The Chi-square value for the cases of idiopathic hypertrophy versus those of endocardial sclerosis was 9, indicating a less marked but still significant difference, the cases of idiopathic hypertrophy having thicker medias.

As mentioned previously, the list of sites of affected arteries in patients with idiopathic hypertrophy must be considered incomplete, because micro-

Table II

LUMEN DIAMETER IN MICRONS	MEDIAN VALUE FOR THICKNESS OF MEDIA IN MICRONS			CORRECTED MEDIAN
	IDIOPATHIC HYPERTROPHY (107 ARTERIES)	ENDOCARDIAL SCLEROSIS (111 ARTERIES)	CONTROLS (111 ARTERIES)	
50-59	14.5	11.0	10.0	10.0
60-69	17.0	13.0	11.0	12.0
70-79	15.0	17.5	12.0	13.0
80-89	18.0	19.0	13.0	14.0
90-109	22.0	18.0	13.0	13.0
110-129	23.0	20.5	12.5	14.5
130-149	26.5	20	14.0	17.0
150-199	26.0	24	20.0	21.5
200-250	41.0	34	18.0	25.5

scopic sections of all organs were not available in all patients. Since coronary artery lesions were seen in all four cases of idiopathic hypertrophy who showed vascular changes, a survey was made of the coronary arteries from 200 consecutive recent autopsies on infants and children. Fourteen patients showed focal intimal fibrosis of one or more coronary arteries. Of these, two had periarteritis nodosa, four severe kidney disease of various causes, and three endocardial sclerosis. Although focal coronary artery intimal fibrosis is not an uncommon incidental finding in infants and children, it thus appears often to indicate the presence of generalized vascular disease of several types. It is of interest that none of the large number of patients with cardiomegaly due to congenital valvular or septal malformations showed such vascular lesions.

COMMENT

The study described demonstrates that some patients with the form of cardiomegaly called idiopathic cardiac hypertrophy (perhaps a majority of such patients) have widespread lesions of muscular and musculoelastic arteries, consisting of diffuse medial muscular hypertrophy and focal intimal fibrosis. Similar but less marked vascular changes are found in some patients with endocardial sclerosis, as has been reported by others.[2] Various generalized vascular diseases can produce microscopically similar intimal lesions. Whether the findings suggest a relation between endocardial sclerosis and idiopathic cardiac hypertrophy cannot be stated, nor can the nature of such a relation, if it exists. It is possible that the two conditions are consequences of the same cause, and are, in a sense, both variations of a disease which produces widespread thickening

of vascular walls. An alternative interpretation is that in both conditions the vascular lesions are somehow either the cause or the result of the cardiomegaly.

The existence of such possible mechanisms renders interpretation of the statistical analysis of the data difficult. A statistically significant difference in arterial medial thicknesses has been demonstrated for the patients with idiopathic cardiac hypertrophy, as compared to those with endocardial sclerosis, and for both these groups as compared to normal control cases. However, whether these differences are due to the fact that the two diseases considered are truly unrelated, or due to the fact that one group of patients demonstrates greater response to a causative agent, or response to a more severe stimulus, cannot be stated. For these reasons, a conservative interpretation of the results of the statistical analysis has been preferred.

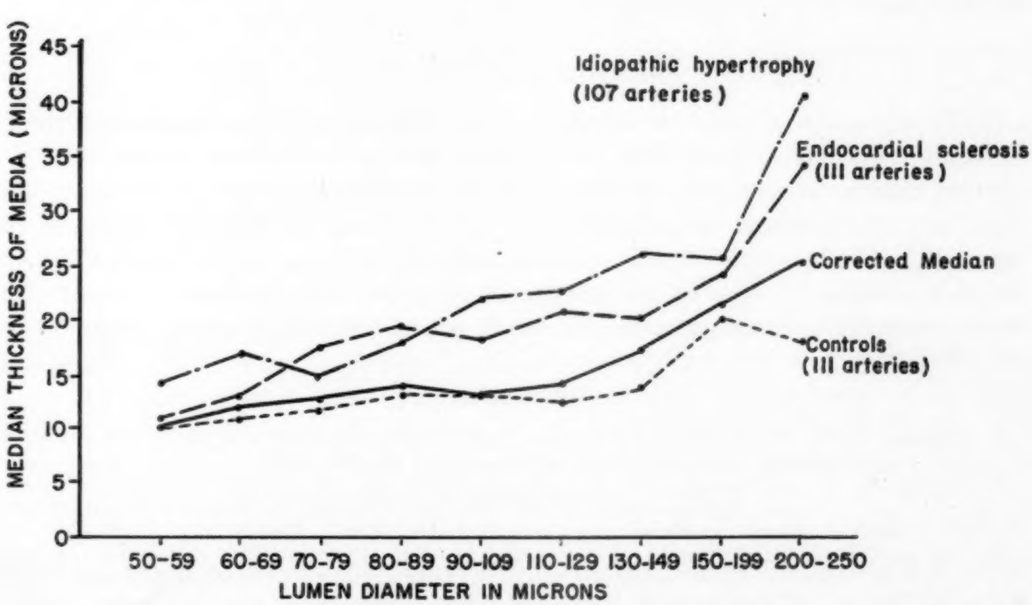


Fig. 4.—Graph of data in Table II showing thickness of medias of arteries of patients with idiopathic hypertrophy and endocardial sclerosis, compared to values for control patients. The corrected median value, as explained in the text, was used for calculation of statistical significance.

The findings do at least suggest that more detailed physiologic study of the vascular systems of patients with idiopathic cardiac hypertrophy might demonstrate functional abnormalities which could shed light on the cause of the cardiac hypertrophy. This opinion is supported by the probable hypertension of the case of this study, and by the report of Dawson and Nabarro.[1] If their patient had not been recognized to have severe hypertension, an interpretation of idiopathic cardiac hypertrophy with generalized vascular disease could properly have been made. Just as cardiac glycogen storage disease,[3] endocardial sclerosis,[4] and the effects of anomalous left coronary artery[5] have been removed from the class of idiopathic cardiac hypertrophy[6-8] as the separate natures of these conditions have been recognized, it may well be that demonstration of a vasophysi-

ologic abnormality (probably most often hypertension) in some patients will result in separation of still another block of cases from this pathogenetically unsatisfying concept.

SUMMARY

Widespread arterial medial hypertrophy and focal intimal fibrosis have been demonstrated in a small group of patients with idiopathic cardiac hypertrophy. The occurrence of similar but less severe lesions in patients with endocardial sclerosis has been demonstrated, and similar intimal lesions have been noted in other types of generalized vascular disease. The implications, that a functional vascular derangement (sometimes if not always hypertension) may explain the cardiomegaly of some patients with idiopathic cardiac hypertrophy and that some relation may exist between this condition and congenital endocardial sclerosis, have been discussed.

SUMMARIO IN INTERLINGUA

Es reportate le casos de 4 infantes con "idiopathic hypertrophia cardiac" associate con extense spissification del media e intima del vasos sanguinee. Un de iste casos es reportate in detalio. Le datos presentate permitte le hypothese que un anormalitate vasophysiologic, possibilemente hypertension—es responsabile pro le cardiomegalia incontrate in alicun casos de "idiopathic hypertrophia cardiac." Nos etiam discute le possibile signification de simile sed minus marcate lesiones vascular in casos de sclerosis endocardial.

REFERENCES

1. Dawson, J. M. P., and Nabarro, Sylvia: A Case of Intimal Hyperplasia of Arteries With Hypertension in a Male Infant, J. Path. Bact. **66**:493, 1953.
2. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of the Heart in Infants and in Young Children With Myocardial Degeneration and Fibrosis (So-called Congenital Idiopathic Hypertrophy), Am. J. Dis. Child. **45**:828, 1933.
3. Landing, B. H., and Bangle, R.: Familial Cardiac Glycogen Storage Disease. Report of 2 Cases and Discussion of Relation to Other Forms of Abnormal Glycogen Deposition, Bull. Internat. M. Mus. **31**:84, 1950.
4. Craig, J. M.: Congenital Endocardial Sclerosis, Bull. Internat. A. M. Mus. **30**:15, 1949.
5. Lyon, R. A., Johansmann, R. J., and Dodd, K.: Anomalous Origin of Left Coronary Artery, Am. J. Dis. Child. **72**:675, 1946.
6. Dammin, G. J., and Moore, R. A.: Cardiac Muscle in Idiopathic Hypertrophy of Heart in Infancy and in Normal Growth, Arch. Path. **27**:122, 1939.
7. MacMahon, H. E.: Hypertrophy of the Heart in Infants, Am. J. Dis. Child. **55**:93, 1938.
8. Race, G. G., and Black-Schaffer, B.: Idiopathic Infantile Hyperplastic and Hypertrophic Cardiomegaly (Congenital Cardiac Hypertrophy), Am. Heart J. **38**:501, 1949.

THE CLINICAL PICTURE OF ENDOCARDIAL FIBROELASTOSIS

Infantile and Childhood Type

E. Grey Dimond, M.D., Frances Allen, M.D., and
Lauren R. Moriarity, M.D.

Kansas City, Kan.

An ENTITY variously labeled as endocardial fibrosis, endocardial fibroelastosis, endocardial sclerosis, and subendocardial fibroelastosis has become well established during the past decade.[9-20] This is evidently the same disease process previously described as fetal endocarditis.[1,2]

The disease and its location suggest that endocardial fibroelastosis is probably the proper title. There seems to be at least two separate disease patterns characterized by this glistening, white, thickened endocardium: One occurring in infants and young children and a second in adult life. Although the pathologic results appear similar in the two age groups, there is sufficient difference in the clinical picture to justify considering endocardial fibroelastosis (infantile and childhood type) as a distinct diagnostic entity.

In the past two years, we have seen nine patients in the first three years of life who died in congestive failure and in whom autopsy revealed endocardial fibroelastosis. In some, congenital cardiac lesions were also present but did not seem sufficient to explain cardiac failure. The entity was correctly recognized in life in four of the nine cases. In a tenth child, still living, the diagnosis has been confirmed by myocardial biopsy. This report describes the clinical findings in this group of nine autopsy-confirmed cases.

At this institution, endocardial fibroelastosis has been the most common cardiac condition associated with death in children below the age of ten. Our patient population is preselected because of its referral nature, and our experience is undoubtedly weighted. However, the following outline is significant:

Deaths under ten years of age (K.U.M.C.)

Total autopsies	154 (100 per cent)
Congenital heart disease	29 (18.8 per cent)
Endocardial fibroelastosis	9 (5.84 per cent of 154) (31 per cent of 29)

Therefore, at this institution, one-third of the children dying of congenital heart disease before the age of ten and on whom autopsies were performed had severe endocardial fibroelastosis.

From the Departments of Medicine and Pathology, University of Kansas Medical Center, Kansas City, Kan.

Presented before the Regional Meeting of the Kansas Chapter of the American College of Physicians, 1954.

Received for publication March 18, 1955.

THE CLINICAL PICTURE

The clinical picture is repetitious and recognizable. A newborn, an infant, or a young child develops respiratory distress. The manifestations are frequently cough, noisy breathing, grunting expiration, flaring of the nostrils, and tachypnea. Very frequently the child has previously been well. These signs of heart failure are usually initially attributed to bronchial pneumonia. The child may die

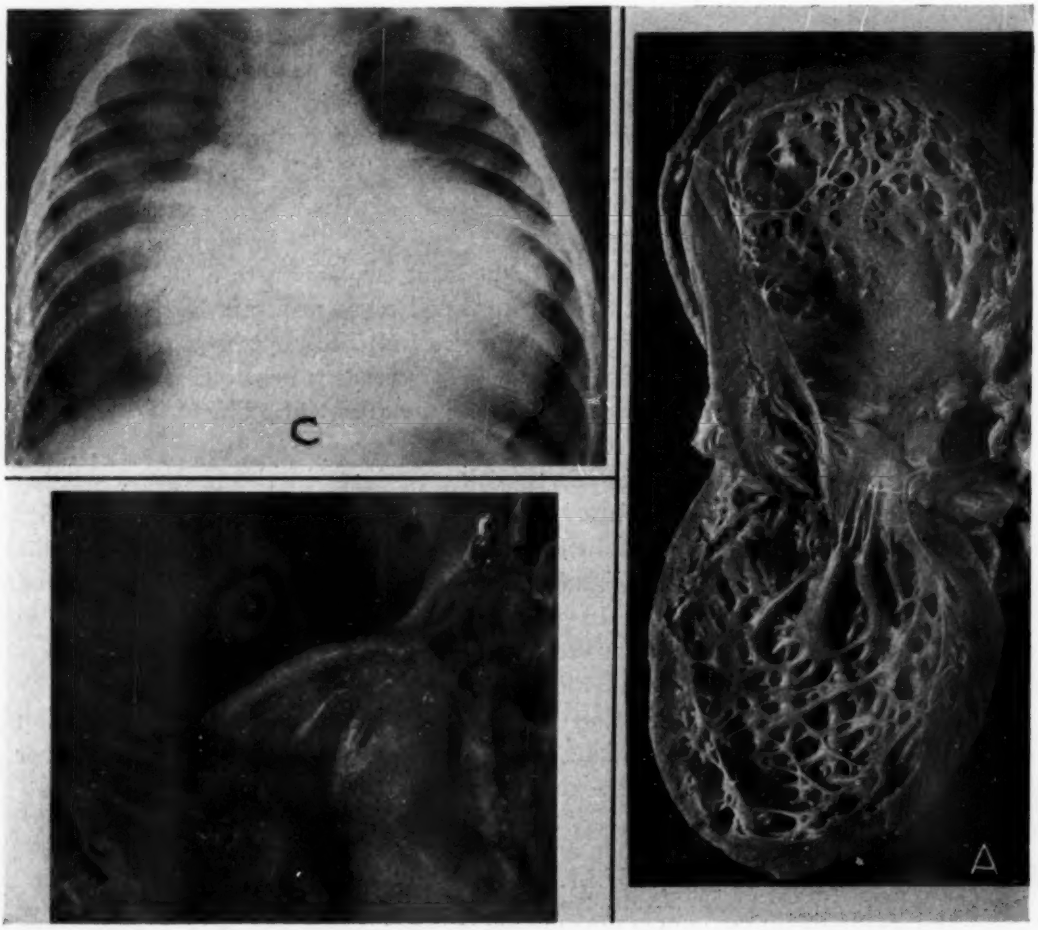


Fig. 1.—*A*, Typical white, glistening thickened endocardium of endocardial fibroelastosis. *B*, Close-up view of thickened mitral valve involved in same endocardial process. *C*, Large globular heart frequently seen in endocardial fibroelastosis.

immediately, after an illness of but a few days (note Case 1) but usually the respiratory difficulties persist, in spite of antibiotics. Because of the persistent respiratory problem, an x-ray of the chest is obtained. This will indicate not only bilateral pulmonary congestion, but an enlarged, globular heart of no specific contour. This is frequently the first suggestion that the heart is involved in the illness. Re-examination of the patient will confirm that a persistent tachycardia is present. The heart sounds are muffled and distant. A

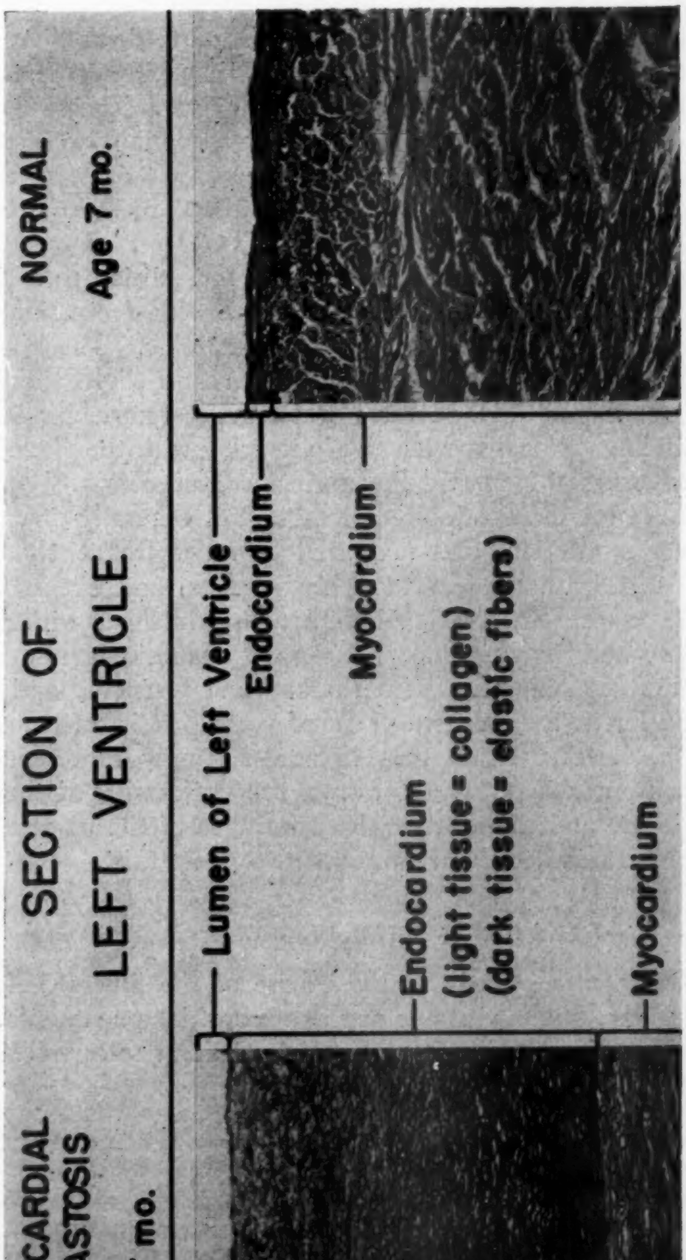


Fig. 2.—Sections of hearts demonstrating altered morphology in endocardial fibroelastosis (left) compared to normal (right). (Verhoeff-Van Gleson stain; × 81).

diastolic gallop rhythm is common. A murmur may or may not be heard (Cases 2 and 3). A tender, large liver and peripheral edema may be found. Occasionally hepatomegaly and ascites are present without edema. An occasional patient will have severe right-heart failure with tricuspid regurgitation manifested by deep systolic jugular pulse and a pulsatile liver. The obvious physical findings of an associated congenital lesion such as a coarctation of the aorta or ductus arteriosus may be present. However, these do not seem adequate to explain the cardiac failure. Pallor and a fall in blood pressure are commonly noted.

The electrocardiogram is usually abnormal. In addition to a sinus tachycardia, the most frequent change is in the T waves with depression, flattening, and sometimes inversion. These changes are nonspecific. The RS-T segment is frequently depressed. P-R interval prolongation and slight widening of the QRS complex are common. Tall peaked P waves suggest auricular involvement. In general, the findings are nonspecific and in keeping with the diagnosis of subendocardial or myocardial ischemia and auricular dysfunction.

The progress of the disease is unpredictable, but generally downhill. Digitalization, sodium restriction, and mercurial diuretics frequently control the cardiac failure. However, the cardiomegaly persists, and eventually cardiac failure and death occur. An occasional child expires in shock with pallor, cold, damp extremities, and hypotension. Moderate cyanosis is not uncommon.

A fair state of compensation, with therapy and restricted activity, occurs in a few children for as long as two or three years. It is, of course, possible that a similar endocardial lesion seen in adults simply represents quiescent or latent disease from childhood. However, the uniformity of the pattern of the childhood picture and the relative disappearance of the disease during the second, third, and fourth decade are arguments against this.

THE DIFFERENTIAL DIAGNOSIS[22-25]

Bronchial Pneumonia.—Early in the course of the illness, before a chest x-ray has been taken, the symptoms suggest bronchial pneumonia. The frequent absence of murmurs makes it particularly difficult to appreciate that the heart may be the underlying cause.

Rheumatic Carditis.—A severe rheumatic pancarditis can mimic the condition. This is especially true in children presenting the signs and symptoms of cardiomegaly, tachycardia, gallop, bizarre murmurs, and cardiac failure. Rheumatic carditis can usually be ruled out because of the absence of typical murmurs, the lack of associated rheumatic phenomena, and normal rheumatic serologic activity studies. Logue and Hurst have set up excellent criteria for this differential diagnosis.[21]

Acute Myocarditis.—Acute myocarditis from infectious causes, diphtheria, mumps, measles, poliomyelitis, pleurisy, influenza, and other diseases can imitate endocardial fibroelastosis and present with cardiomegaly, tachycardia, tachypnea, gallop rhythm, unusual murmurs, heart failure, and an abnormal electrocardiogram. The recognition of the underlying disease should provide

the necessary differential evidence. Actually, in our experience, cardiac failure in the very young is rarely from these causes and is frequently due to endocardial fibroelastosis.

Fiedler's Myocarditis.—The entity previously labeled as Fiedler's myocarditis probably should be included in the group discussed in the previous paragraph. In our experience, the entity of Fiedler's myocarditis is extremely rare, and the term probably should be restricted to a myocarditis, possibly of virus origin.

Paroxysmal Auricular Tachycardia of Infancy.—In those children in whom a paroxysmal arrhythmia is prolonged and accompanied by cardiac dilatation and signs of cardiac failure, differential diagnosis may be extremely difficult. Electrocardiographic examination may aid, and the response to vagotonic maneuvers and drugs, especially rapid digitalization, is probably the most useful differential item. Actually, the initial presenting picture of a child in severe respiratory distress with a rapid heart rate and cardiac enlargement requires digitalization and treatment first and precise diagnosis later.

Glycogen Storage Disease.—From our experience, glycogen storage disease with cardiac involvement and heart failure must be very rare.

CASE REPORTS

CASE 1.—G. L. A. No. 51-27746, 10-month-old, white, male infant was admitted to University of Kansas Medical Center on July 8, 1951, and expired on July 10, 1951.

History: Birth weight 7½ pounds, full-term normal delivery, uncomplicated pregnancy. Development normal until 3 months of age at which time the baby had "bronchitis and asthma" and was hospitalized for five weeks. In the month preceding admission baby "caught cold" and developed a cough without fever or coryza. One week prior to admission the infant had a severe coughing and crying episode and "went limp" for fifteen to twenty seconds and was very cyanotic. The following day the feet and ankles began to swell, oxygen was given, the patient was digitalized, moderate improvement lasted for 24 hours. He was then transferred to this hospital for diagnostic study.

Examination demonstrated a fairly well-developed child who was crying and irritable with cyanosis of hands and feet. Chest was symmetrical, expansion equal, some sternal retraction. The left-heart border was at the axillary line with a diffuse, heaving apex thrust. A Grade 3 systolic murmur was heard best along the left sternal border and was transmitted over the entire precordium. A systolic thrill was present. The liver was firm, two fingerbreadths below the right costal margin. The spleen was palpable. There was slight pitting edema over the sacrum and feet. ECG indicated right-axis deviation (this was not considered as evidence of right ventricular hypertrophy in view of the child's age). X-ray showed the heart to be above limits in size and globular in contour. The lung fields and the hilar markings were exaggerated. The child was maintained on oxygen and digitalis and died suddenly two days after admission.

Anatomical findings: Heart weighed 70 grams, foramen ovale was patent, and a patent ductus was present. Myocardium of the right auricle measured 3 mm.; right ventricle, 8 mm.; left auricle, 1 mm.; and the left ventricle, 6 mm. The endocardial surfaces of the right ventricle and left auricle were diffusely thickened and white and opaque in color. The endocardial surface of the left ventricle, however, was only slightly changed grossly. Endocardial thickening of the right auricle and ventricle and left auricle was seen to involve the papillary muscles and the tricuspid valve.

Summary: This 10-month-old child developed heart failure; at autopsy marked endocardial thickening of the right auricle, right ventricle, and left

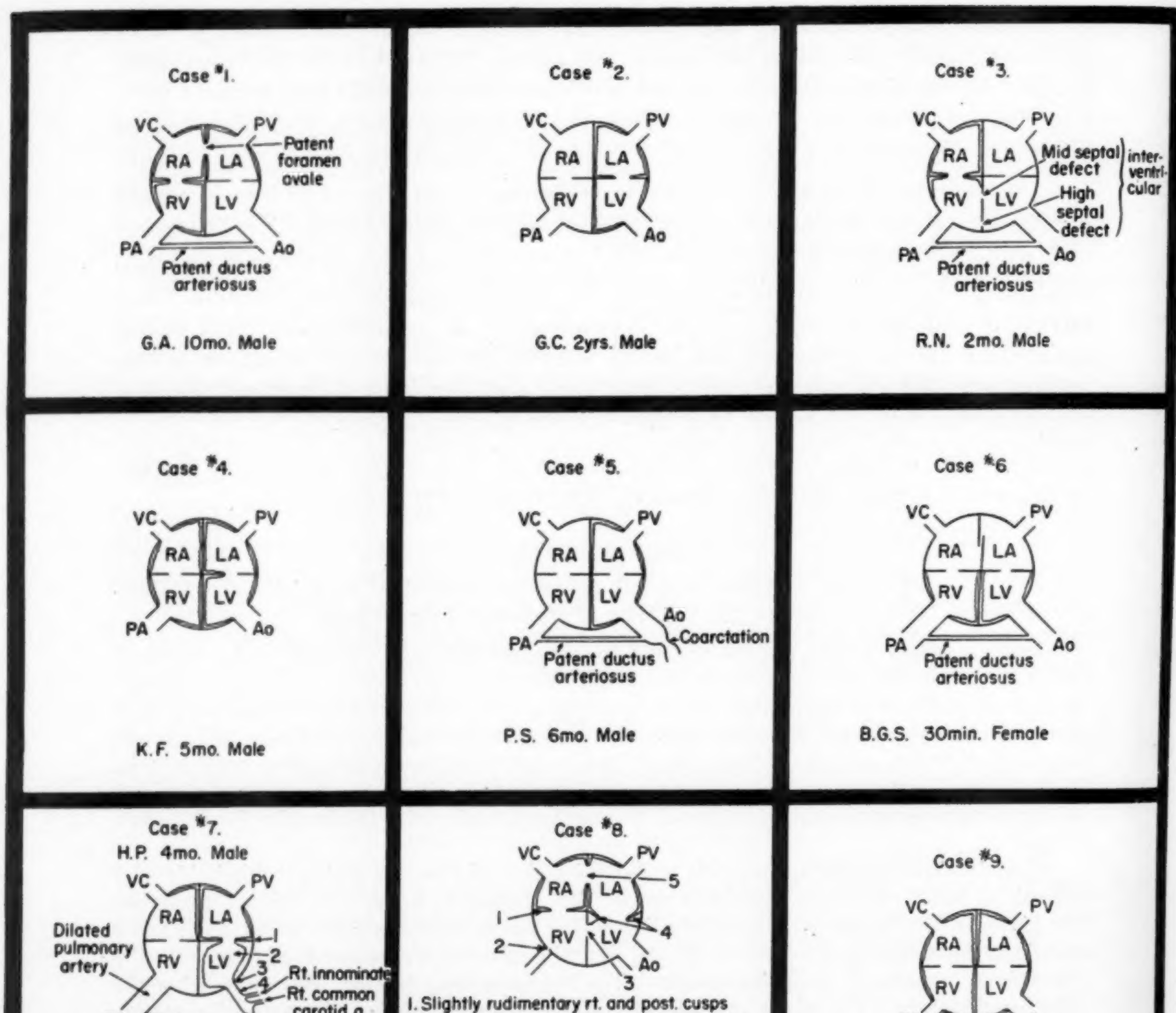


Fig. 3.—Diagram indicating site of pathology in each of the nine cases. Location of endocardial lesion indicated by corrugated line. Associated congenital lesions indicated.

auricle was present. The left ventricle was very slightly involved. The child survived 9 days after the onset of symptoms.

Case 2.—G. C. No. 52-12500. This 2-year-old white male twin was admitted to the University of Kansas Medical Center on Nov. 2, 1952, and expired on the same day. This child was considered well until ten days prior to admission. He was the first of fraternal (not identical) twins. He had never had cyanosis or dyspnea until the onset of the present illness. He had developed normally, walking at 1 year and talking at 14 months. Ten days prior to admission he developed a nasal discharge and slight fever. A diagnosis of "flu" was made. Two days later a chest x-ray was done, a diagnosis of pneumonia was made, and the patient was hospitalized. After 4 days of receiving penicillin he was afebrile and returned home. Upon returning home he developed dyspnea and puffiness of the face and ankles. The attending physician thought that the heart was beginning to enlarge and referred him to the hospital.

Examination revealed a critically ill, well-developed, well-nourished child with marked dyspnea, pallor, and cyanosis of the mucous membranes. One-plus edema of the extremities was noted. The respirations were labored, shallow, and fast. Coarse rhonchi were heard over the chest. The heart was markedly enlarged, but without thrills or murmurs. Heart rate was 180; the tones were muffled; there was a gallop rhythm. The liver was 6 to 7 cm. below the right costal margin. Electrocardiogram showed marked right-axis deviation with the mean QRS vector at 150°. The T waves were inverted at V_5 and V_6. Chest x-rays showed generalized cardiac enlargement.

The child was given oxygen and digitalized; however, he expired in 12½ hours.

Anatomical findings: Heart weight, 170 grams; left ventricular wall 10 mm. thick, and right ventricular wall 3 mm. The endocardial surfaces of the left ventricle and auricle were glistening, opaque, and white. The valves were normal; there was no ductus arteriosus and the foramen ovale was not patent. The myocardium had a number of small foci of lymphocytes and rare polymorphonuclear leukocytes. Generally in the region of these foci there were small areas of muscle atrophy and regeneration.

Summary: This child was a fraternal twin who was well and healthy until 10 days prior to death. No valve lesions were present, and his endocardial lesions were confined to his left ventricle and left auricle. The child survived 12 days from the onset of symptoms.

Case 3.—R. N. No. 53-692. This 2-month-old Negro infant was admitted to the University of Kansas Medical Center on Jan. 22, 1953, and expired on April 1, 1953. The baby weighed 5 pounds at birth and on admission weighed 6 pounds, 10 ounces. There had been an uncomplicated pregnancy, although the mother had had penicillin treatment for syphilis two years previously with a subsequent negative serology. The infant had eaten poorly since birth and 1 week before admission had developed fever, cough, and rapid respirations.

Examination revealed a poorly developed, thin, Negro child with respirations of 40 to 45 per minute. Fine moist râles were heard over the entire chest. A Grade 2 systolic murmur could be heard to the left of the sternum in the second and third intercostal spaces. Femoral pulsations were present; there was no cyanosis. Heart rate varied between 140 and 160. There was moderate cardiac enlargement. Serial electrocardiograms were normal other than sinus tachycardia. X-ray showed moderate cardiac enlargement and congestion of the lung fields. The child was fairly comfortable as long as he was in an oxygen tent. He ate poorly and was very weak when out of oxygen. Digitalis only slightly improved him. Repeated febrile episodes with pulmonary infection were suffered. General course was downhill. It was felt that the child might have an aortic pulmonary window or a large patent ductus and because of his grave condition it was decided to attempt surgical repair. He died on the table after the pericardial sac was opened.

Anatomical findings: Multiple anomalies of the heart were present. In the upper membranous portion of the intraventricular septum there was a small defect measuring about 2 mm.

in diameter and just beneath this there was a considerably larger one measuring about 4 mm. in diameter. There was also a small patent ductus arteriosus. Endocardial fibroelastosis of both auricles and the upper right ventricle involving the tricuspid valve was present. The heart weighed 60 grams.

Summary: This 2-month-old Negro child had had continuous respiratory difficulty since birth. Diagnosis of an aortic pulmonary window or patent ductus arteriosus was made and the child expired during surgery. Endocardial fibroelastosis involving both auricles and the upper one-half of the right ventricle was found as well as a patent ductus and two ventricular septal defects. The infant survived 3½ months after the onset of symptoms.

CASE 4.—K. M. F. No. 53-2357. This 5-month-old male infant was admitted to the University of Kansas Medical Center on Feb. 17, 1953, and was dismissed on Feb. 21, 1953. One month prior to admission at the age of 4 months the patient began having increased respiratory rate and expiratory grunting. After 10 days this became severe and was accompanied by cyanosis. He was admitted to another hospital. X-ray study indicated a large heart, and physical examination showed a large liver. The patient was digitalized and given oxygen and transferred to this hospital. Examination of the heart revealed a rate of 130; no murmurs were heard; the liver was palpable two fingerbreadths below the costal margin. Electrocardiogram indicated a sinus rhythm of 130 per minute and inverted T waves in Leads I, V_3, and V_5. Under therapy, the child became compensated, but the heart remained large, and he was dismissed on the fourth hospital day.

Seven weeks later, at the age of 7½ months the child was readmitted to the hospital. Grunting respirations had started on the day of admission. X-ray examination showed considerably greater cardiac enlargement. Respirations were 50 per minute with expiratory grunts. The heart was massively enlarged. There was a gallop rhythm present. The liver was 3 to 4 cm. below the right costal margin. The child was placed in oxygen, given further digitalis and antibiotics, but expired 21½ hours after admission.

Anatomical findings: Severe endocardial fibroelastosis of the left auricle and left ventricle and a lesser involvement of the right auricle and the right ventricle were found. Fibrous thickening of the anterior leaflet of the mitral valve was also present. Heart weighed 120 grams. The myocardium of the left ventricle measured 1 cm. in thickness. There were no significant valvular or great vessel lesions present.

Summary: This child had been completely well until four months of age at which time respiratory difficulties began followed by cardiac failure. At autopsy the most striking finding was the marked cardiac enlargement. The endocardial lesions were most severe in the left auricle and left ventricle but were also present in the right auricle and right ventricle. There were no other congenital lesions present. This infant survived 3½ months after the onset of symptoms.

CASE 5.—P. S. No. 53-315. This 5-month-old male infant was admitted to the University of Kansas Medical Center on Jan. 1, 1953, and dismissed on Jan. 20, 1953. This patient was born after a 7-month gestation with a birth weight of 4½ pounds. The baby was in oxygen the first three days of life because of prematurity. A postnatal jaundice lasting two weeks occurred. In the first 5 months of life, the child had three hospitalizations for upper respiratory infections. Three days prior to this admission the child started to cough and breathe rapidly and developed a fever of 100.4°.

Physical examination revealed a poorly developed, poorly nourished infant with cyanosis, expiratory grunting, and crying. Heart rate was 160; no murmurs could be heard; the tones were muffled. A firm liver was felt two fingerbreadths below the costal margin. Electrocardiogram indicated S-T depressions in Leads I, II, III, aV_F, and V_5. The child was digitalized and improved and was released from the hospital 4 weeks after admission. He remained fairly well

at home for 1 week; and then respiratory difficulty began quickly, and he was rushed to the hospital where he died 18 hours after admission.

Anatomical findings: Severe fibroelastosis of the left auricle and left ventricle. Heart weighed 90 grams. There was a coarctation of the aorta and a patent ductus arteriosus. Hypoplasia of the left lung was present. The right ventricle measured 5 mm. in thickness; the left ventricle, 1 cm. Aortic valves were bicuspid.

Summary: This child had multiple congenital anomalies, the principle of which was severe fibroelastosis on the left auricle and left ventricle. There was also a bicuspid aortic valve, a coarctation of the aorta and a patent ductus arteriosus.* The infant survived 6 weeks after the onset of symptoms.

CASE 6.—B. E. S. This infant girl was born prematurely on July 26, 1953. The mother was a 23-year-old primigravida who was RH positive and had never received a blood transfusion. Serologic tests for syphilis were negative. Prenatal course was normal until 2 days prior to delivery at which time the mother began to have abdominal pain and backache. The infant was born spontaneously. After the membranes ruptured, the fetal heart tones were found to be 154 per minute. During the second stage of labor, the fetal heart was noted to be slow and irregular. At the birth, the infant was noted to have marked ascites, respirations were gasping in nature and infrequent. The baby's heart stopped after 25 to 30 minutes of life.

Anatomical findings: Heart weighed 12 grams. There was a patent ductus arteriosus and a large patent foramen ovale. There was marked fibroelastosis of the right and left ventricles. There was acute and chronic passive congestion of the spleen, liver, and kidneys, a bilateral hydrothorax (50 c.c.), ascites (400 c.c.), and edema of the lower extremities.

Summary: This is evidently an example of in utero cardiac failure. The single cardiac lesion which seemed to be severe enough to account for this was fibroelastosis. The infant died in heart failure 30 minutes after birth.

CASE 7.—H. G. P. No. 53-9110. This 3-month-old white male infant was admitted to the University of Kansas Medical Center on July 22, 1953, and expired on Aug. 12, 1953. This patient was born by cesarean section (due to maternal pelvic deformity), cried spontaneously, but had been blue since birth. Three days prior to admission he had had three "spells" of momentary duration, characterized by stiffening and rolling of the eyes. These episodes were followed by extreme irritability and poor eating. The next day he had ten of these episodes and was hospitalized. He was subsequently admitted here for study and therapy. Inspection revealed a striking demarcation of cyanosis following the left side of the thorax, the left hand, the lower trunk, and both lower extremities. The right side of the thorax and the right hand were normal. The head and neck were somewhat cyanotic, but not so marked as in the other areas. A soft, Grade 1 systolic murmur was heard over the left sternal border. Pulmonary second sound was normal. Femoral pulses were palpable. Blood pressure readings in the extremities were (systolic only) right arm 50, left arm, 40, right leg 40, left leg 40 mm. Hg. There was no edema. Electrocardiogram indicated a rate of 210 per minute. There were tall peaked, slightly notched P waves in Leads II and aV_F. There were tall QRS complexes over the left chest suggesting left ventricular hypertrophy. No T wave or S-T segment changes were noted. The chest plate showed no particular cardiac enlargement. There was considerable prominence of the pulmonary outflow track. Lung fields were clear. Clinical impression was that this was an infantile coarctation with retrograde flow through a patent ductus below the site of coarctation.

On Aug. 11, 1953, the child was taken to surgery and a thorocotomy was performed. At surgery, a hypoplastic ascending aortic arch giving off two innominate arteries was found. A distal aortic arch connected by a large patent ductus arteriosus to an enlarged pulmonary artery

*We are indebted to Dr. Russell Kerr, pathologist, Saint Joseph Hospital, Kansas City, Missouri, for the information regarding this autopsy and for the contribution of this heart for study.

was found. Trial clamping of the ductus with a Blalock clamp resulted in some diminishing of the aortic pulsation. No attempt at corrective surgery was made, and the operation was terminated without difficulty. Post-operative course the first 20 hours was uneventful. The child then developed respiratory difficulty and died.

Anatomical findings: Hypoplasia of the left ventricle (1 by 1½ by 1½ cm.), diffuse narrowing of the arch of the aorta, and a large patent ductus arteriosus. Severe fibroelastosis of the left ventricle and left auricle and a moderate degree of fibroelastosis of the right auricle. A bicuspid aortic valve was present with thickening of cusps and fusion of the commissures resulting in stenosis. There was also a stenosis of the mitral valve. A patent ductus measured 15 mm. in diameter. There was no fibroelastosis in the right ventricle.

Summary: Multiple congenital anomalies were present in this child with a hypoplasia of the entire left heart and the aortic arch. The principal circulation to the lower extremities was by way of reverse flow through a patent ductus arteriosus. The aortic valve was bicuspid and severely stenosed as was the mitral valve. The infant survived 3 weeks following the onset of symptoms.

CASE 8.—R. L. No. 52-7765. This 3-month, 7-day-old infant was admitted to the University of Kansas Medical Center on July 12, 1952, and died 15 hours after admission. The child was known to have a heart murmur at birth and had been cyanotic since birth. He also had a left clubfoot. One week prior to admission, the patient developed a cough; 2 days before admission parents noted an increasing cyanosis and increased respiratory rate with grunting. The mother had had a 4-day acute febrile illness diagnosed as "flu" when she was one-month pregnant.

Physical examination revealed a cyanotic well-developed, well-nourished child who was in acute respiratory distress. There were no râles. A systolic murmur was heard over the entire chest. The liver was palpable 3 fingerbreadths below the right costal margin. Continuous oxygen was given, and the child's respirations and color seemed to improve, when he died suddenly 15 hours after admission.

Anatomical findings: Heart weighed 90 grams; there was an atrial septal defect 1 cm. in diameter. Tricuspid valve appeared normal. There was an interventricular septal defect 1 by 1½ cm. Pulmonary artery was hypoplastic, and the pulmonary valve was stenotic. There was great thickening of the subendocardial tissues of the right and left auricle, and this thickening extended down into the left ventricle involving the mitral valve. The right ventricle was markedly hypertrophied.

Summary: This child developed respiratory symptoms one week prior to death. At autopsy the principal lesions were pulmonary stenosis, hypoplasia of the pulmonary artery, auricular septal defect, ventricular septal defect, and severe endocardial fibroelastosis of the right auricle, and moderate degree of the left auricle. This infant survived 5 days after the onset of symptoms.

CASE 9.—M. S. No. 53-10900. This 2½-year-old Negro boy was admitted to the University of Kansas Medical Center on Sept. 29, 1953, and dismissed on October 28, 1953. He had been well until 5 weeks prior to admission when he suffered an upper respiratory infection with prolonged recovery. One week following this illness his mother noted he had an enlarged abdomen. He vomited several times and was given antibiotics. The doctor then noted an abdominal mass. A kidney tumor was suspected, and he was hospitalized for diagnostic measures. Because of difficulty in cystoscoping the patient, he was sent to the University of Kansas Medical Center for definitive urologic diagnosis.

Physical examination: The patient was a well-developed, well-nourished male weighing 36 pounds. The heart rate was 140. No murmurs were heard. The abdomen was distended with a smooth large mass which was thought to be the liver. Electrocardiogram showed huge biphasic complexes with inverted T waves. Chest x-ray indicated cardiac enlargement. The initial impression was that this might be glycogen-storage disease. A biopsy of the liver showed chronic

passive congestion, but no glycogen-storage. The child developed a sore throat which responded to penicillin treatment. One month after initial admission re-examination of the heart by fluoroscopy showed that it was considerably enlarged. The heart tones were noted to be soft and muffled, and a Grade 1 soft systolic murmur could be heard along the left sternal border. The patient was digitalized, placed on a salt-restricted diet, and followed in the Outpatient Clinic. During the following weeks the child vomited occasionally and complained of abdominal discomfort. His heart tones remained muffled. On Dec. 10, 1953, the patient had nausea and vomiting which lasted for 3 or 4 days. He then developed acute congestive heart failure with collapse. Therapy was ineffective, and he died on Dec. 14, 1953, four months after the onset of his illness.

Anatomical findings: The heart weighed 145 grams. There was tremendous hypertrophy and dilatation. The endocardium of all four heart chambers was markedly thickened and white. There was a severe tricuspid insufficiency with a tricuspid valve measuring 105 mm. Microscopic examination of the heart revealed changes not recognized in the gross examination; just beneath the thickened endocardium numerous areas of myocardial degeneration were found. These areas of myocardial necrosis were patchy in distribution, but most common just beneath the endocardium and least frequent nearest the epicardium. The coronary arteries were patent. These necrotic areas were found in the walls of all four chambers of the heart.

Summary: This child was originally suspected of having either a kidney tumor or glycogen-storage disease. Some 4 months after the onset of the respiratory illness he died in heart failure and shock. Not only did he have severe endocardial fibroelastosis, but also patchy necrotic areas just beneath the endocardium.

DATA ANALYSIS

The sex ratio in our cases has been interesting, eight males to one female. The race distribution is unreliable because of the selection of our material. We have seen seven whites to two Negroes. One of our patients, Case 6, evidently is an example of congestive heart failure in utero. The duration of symptoms from onset to death varied from 30 minutes to 10 months. Dyspnea was present in eight of the nine cases, cyanosis was present in six cases, cough was a severe symptom in four cases, shock was present in three cases, sudden death occurred in three cases. The accompanying tables graphically express the data of our cases.

CONCLUSION AND SUMMARY

Endocardial fibroelastosis is a common condition which can be recognized ante mortem. Unexplained and unexpected respiratory distress occurring in an infant or child may be the earliest symptom. Cardiac enlargement and evidences of congestive failure, with or without a murmur, without other adequate evidence of heart disease, should suggest the entity. Improvement may occur under treatment, but this is only temporary and death eventually results.

CONCLUSION E SUMMARIO IN INTERLINGUA

Fibroelastosis endocardial es un condition commun que es recognoscibile ante morte. Inexplicate e inexpectate angustia respiratori in infantes o juveniles pote esser le prime symptoma. Allargamento cardiac e signos de dysfunctionamento congestive con o sin murmure justifica le suspicion de fibroelastosis endocardial in casos non characterisate per altere signos adequate de morbo cardiac. Melioration occurre a vices sub tractamento, sed isto es temporari, e morte adveni in le curso del tempore.

Appendix

Table I

	GLA	GC	RN	KMF	PS	BGS	HP	RL	MS
Case No.	1	2	3	4	5	6	7	8	9
Sex	M	M	M	M	M	F	M	M	M
Race	W	W	C	W	W	W	W	W	C
Date of death	7/10 51	11/3 52	4/1 53	4/14 53	1/28 52	7/26 53	8/12 53	7/12 52	12/14 53
Age onset	Birth	2 Yr.	2 Mo.	4 Mo.	5 Mo.	Birth	Birth	Birth	2 Yr. 5 Mo.
Duration	10 Mo.	10 Da.	2½ Mo.	3½ Mo.	1 Mo.	30 Min.	3½ Mo.	3 Mo.	4 Mo.
Age death	10 Mo.	2 Yr.	4½ Mo.	7½ Mo.	6 Mo.	30 Min.	3½ Mo.	3 Mo.	2 Yr. 9 Mo.

Table II

SYMPTOMS	1	2	3	4	5	6	7	8	9
Dyspnea	+	+	+	+	+	+	+	+	o
Cyanosis	+	+	o	o	+	+	+	+	o
Orthopnea	+	−	−	o	o	−	o	o	o
Cough	+	+	+	+	+	+	o	o	o
Vomiting	o	o	o	o	+	o	o	+	+
Convulsion	o	o	o	o	o	o	+	o	o
Shock	+	o	o	o	+	+	o	o	+
Sudden death	+	+	o	o	o	+	o	+	o

+—Present
o—Absent
+ —Information not given

TABLE III

PHYSICAL FINDINGS	1	2	3	4	5	6	7	8	9
Tachycardia	+	+	+	+	+	o	+	+	+
Tachypnea	+	+	+	+	+	o	+	+	+
Râles	o	+	+	+	+	+	o	o	o
Murmurs	+	o	+	+	o	+	+	+	o
Liver enlargement	+	+	+	o	+	+	o	+	+
Edema	+	+	o	o	o	+	o	o	+
Cyanosis	+	+	o	+	+	+	+	+	o
Cardiomegaly (by P_x)	+	+	+	+	+	−	+	+	+
Thrills	o	o	o	o	o	−	o	+	o

TABLE IV

X-ray	1	2	3	4	5	6	7	8	9
Cardiomegaly	+	+	+	+	+	+	+	+	+
Lung pathology	o	+	+	o	+	−	o	−	o
ECG T wave or S-T segment changes	+	+	o	+	+	+	o	−	+
Conduction defects	o	o	o	o	o	+	o	+	o
Correct ante-mortem diagnosis	o	+	o	+	+	o	o	o	+

TABLE V

AUTOPSY GROSS Chambers involved	1	2	3	4	5	6	7	8	9
RA	+	o	+	+	o	o	+	+	+
RV	+	o	+	+	o	+	o	o	+
LA	+	+	+	+	+	o	+	+	+
LV	o	+	o	+	+	+	+	+	+
Valves involved									
Tricuspid	+	o	+	o	o	o	o	+	o
Pulmonic	o	o	o	o	o	o	o	o	o
Mitral	o	o	o	+	o	o	+	+	o
Aortic	o	o	o	o	o	o	+	o	o

TABLE VI

	1	2	3	4	5	6	7	8	9
Heart weight (grams)	70	170	60	120	90	12	46	70	145
Normal heart weight (grams)	39	56	28	29	31	12	25	25	56
Other anomalies									
Patent ductus	+	o	+	o	+	+	+	o	o
Patent foramen ovale	+	o	o	o	o	+	o	o	o
ASD	o	o	o	o	o	o	o	+	o
VSD	o	o	o	o	+	o	o	+	o
Hypoplasia of aorta or coarctation of aorta	o	o	+	o	o	o	+	o	o
Microscopic findings									
Endocardial thickening	+	+	+	+	+	+	+	+	+
Myocardial extension	+	+	+	+	o	o	+	+	+
Myocardial fiber hypertrophy	+	+	+	+	+	o	+	+	+
Myocarditis	o	+	o	o	o	o	o	o	o

REFERENCES

1. Gross, Paul: Concept of Fetal Endocarditis—A General Review With Report of an Illustrative Case, Arch. Path. **31**:163, 1941.
2. Kerr: Report of Case of Pericarditis and Endocarditis in a Child Nineteen Months Old, Medical Examiner **2**:102, 1839.
3. Dennis, James L., Hansen, A. E., and Corpening, Thomas N.: Endocardial Fibroelastosis, Pediatrics **12**:130, 1953.
4. Farber, Sidney, and Hubbard, John: Fetal Endomyocarditis: Intrauterine Infection as a Cause of Congenital Cardiac Anomalies, Am. J. M. Sc. **186**:705, 1933.
5. Peale, Augustin R., and Lucchesi, Pascal F.: Report of a Case of Measles Encephalitis Complicated by So-Called Fetal Endocarditis and Gonorrheal Pyosalpinx, Am. J. Clin. Path. **12**:357, 1942.
6. Craig, John M.: Congenital Endocardial Sclerosis, Bull. Internat. A. M. Mus. **30**:15, 1949.
7. Gowing, N. F. C.: Congenital Fibroelastosis of the Endocardium, J. Path. & Bact. **65**:13, 1953.
8. Collier, Fred C., and Rosahn, Paul D.: Endocardial Fibroelastosis, Report of Two Cases, Pediatrics **7**:175, 1951.
9. Blumberg, Richard W., and Lyon, Robert A.: Endocardial Sclerosis, A.M.A.J. Dis. Child. **84**:291, 1952.
10. Adams, Forrest H., and Katz, Benjamin: Endocardial Fibroelastosis—Case Reports With Special Emphasis on the Clinical Findings, J. Pediat. **41**:141, 1952.
11. Davis, J. N.: Malnutrition—The Most Frequent Cause of Endocardial Sclerosis, M.D. Thesis, Bristol.
12. Powers, Grover F., and LeCompte, Philip M.: Remarks on a Case of Congenital Idiopathic Hypertrophy of the Heart, J. Pediat. **12**:760, 1938.
13. Hill, Wm. T., and Reilly, Wm. A.: Endocardial Fibroelastosis, A.M.A. Am. J. Dis. Children **82**:579, 1951.
14. Sano, M. E., and Anderson, N. A.: Elastic Tissue Hyperplasia of the Endocardium, Arch. Path. **33**:533, 1942.
15. Cosgrove, G. E., Jr., and Kaump, D. H.: Endocardial Sclerosis in Infants and Children, Am. J. Clin. Path. **16**:322, 1946.
16. Benjamin, B., and Simon, M. A.: So-Called Congenital Idiopathic Hypertrophy of the Heart, A.M.A. Am. J. Dis. Child. **59**:842, 1940.
17. Weinberg, T., and Himmelfarb, A. J.: Endocardial Fibroelastosis (So-Called Fetal Endocarditis), Bull. Johns Hopkins Hosp. **72**:299, 1943.
18. Stadler, H. E., Rein, Chas. A., and Friedman, H. P.: Prenatal Fibroelastosis (Fetal Endocarditis)—Manifested Clinically by Total Heart Block, J. Pediat. **36**:370, 1950.
19. Edmonds, Henry W., and Seelye, Walter B.: Endocardial Sclerosis—Review of Changing Concepts With Report of Six Cases, Pediatrics **7**:651, 1951.
20. Johnson, Frank R.: Anoxia as a Cause of Endocardial Fibroelastosis in Infancy, Arch. Path. **54**:237, 1952.
21. Logue, R. B., and Hurst, J. W.: Rheumatic Fever During the First Few Years of Life and its Differentiation From Endocardial Fibrosis, Am. J. M. Sc. **223**:648, 1952.
22. Kugel, M. A.: Enlargement of the Heart in Infants and Young Children, AM. HEART J. **17**:602, 1939.
23. Mahon, Geo. S.: Idiopathic Hypertrophy of the Heart and Endocardial Fibrosis, AM. HEART J. **12**:608, 1936.
24. Eigel, Edwin G., and Lynxwiler, C. P.: Cardiac Enlargement in Infancy, Arch. Pediat. **63**:433, 1946.
25. Kenney, F. E., and Sanes, S.: Dilatation and Hypertrophy of the Heart in Infancy Due to Parencyhmatous Myocarditis, J. Pediat. **3**:321, 1933.

STUDIES OF THE ATRIOGRAM

J. Stephanopoli de Comnène, M.D., B. Bladier,
F. Colombani, M.D., and J. Bonifaci, M.D.

Marseille, France

INTRODUCTION

STANDARD treatises give but little information about the atriogram, so that there is the temptation to amplify the image of the P wave and study it with the object, first, of defining more accurately the already known aspects of the P wave; then, in the face of the impossibility of getting first-hand knowledge of the phenomena of the auricular sinus node, of trying to work out at least such conditions as will make that knowledge possible. We have, therefore, tried to work out that program in the following manner. We have first recorded with Bladier's instrument the normal atriogram, then atriograms of chronic cor pulmonale, atriograms of mitral stenosis, and atriograms of flutter and fibrillation. In a second stage we have tried to analyze the curve thus recorded through the study of the derived functions of such curves drawn graphically, assuming that it would thus be possible to come to a determination of the sinus phenomenon itself. In work still in progress, we are perfecting the simultaneous recording of both the P wave and its derived function and their experimental application from our point of view. We have been helped in our task by the fine achievements of Rijlant and Pruche with regard to the amplification of P, and those of Meyer-Heine and Jammet with regard to the analysis of these curves.

THE APPARATUS

The apparatus properly speaking has been conceived and set up by Bladier and has already been the subject of many articles. Let it be recalled that the patient is placed in a Faraday cage fitted with a preamplifier. The operators work in an adjoining dark room with an apparatus consisting of (a) a two-stage amplifier of tension, supplied with current from the mains (110 volts, 50 c.p.s.) after rectifying and filtering; (b) a cathrode-ray oscillograph; (c) the time base; (d) a film reel from which the film reels vertically at the rate of 15 cm. per second.

Working in such conditions, we realize a gain of about 400,000, and we can vary it when required, as the process of recording is going on. The time

Received for publication Feb. 21, 1955.

constant was set at about 0.6 sec., since Bladier demonstrated in previous works that this is sufficient to avoid any distortion even in pathologic waves.

RECORDINGS

A. Normal P Waves.—The recording is not different from that of pathologic P waves. It has been carried out from two precordial unipolar leads, which we call E13 and E18, connected according to the usual method with the central terminal of Wilson.

The positions E13 and E18 are defined, at the times when the pulmonary x-ray examination takes place, as follows: E13 is marked on the skin at the point of projection placed on the x-ray screen, 2 cm. to the inner side of the right end of the largest horizontal diameter of the right auricle. E18 is marked on the skin at the point of projection of the major ventricular axis, situated 3 cm. to the inner side of the cardiac apex. In such positions the normal P waves recorded are monophasic as shown in Fig. 1. It will be noticed that the tracing,

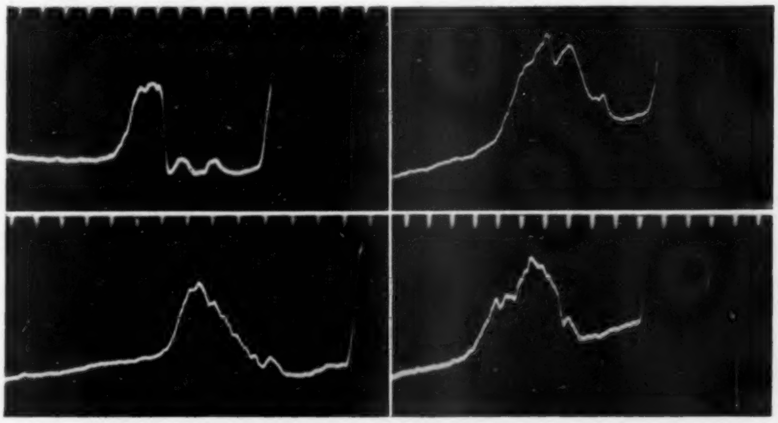


Fig. 1.—Normal P waves. The sensitivity employed for each recording represents a deflection of about 15 mm. for 40 microvolts.

Fig. 2.—Auriculoventricular dissociation.

which we know from experience to be technically satisfactory and therefore devoid of any artifacts, evinces many slight deflections, some of which are remarkably constant, but upon which we do not mean to enlarge in the present work.

B. Pathological P Waves.—Fig. 2 shows the recording of the P wave in the course of an auriculoventricular dissociation. It shows not only a diphasic

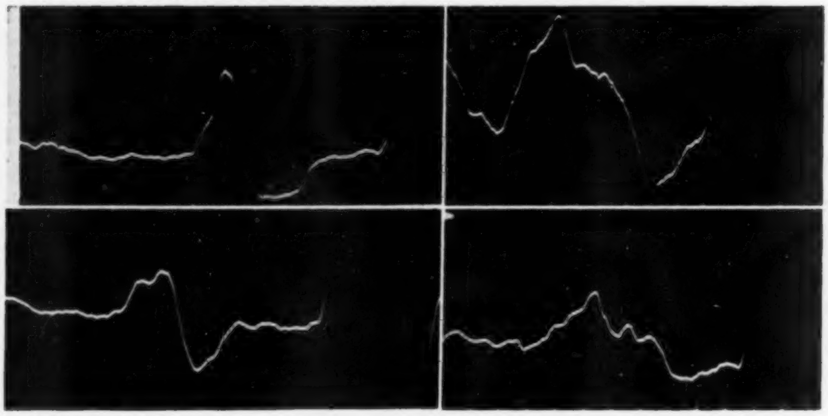


Fig. 3.—Pulmonary P waves.

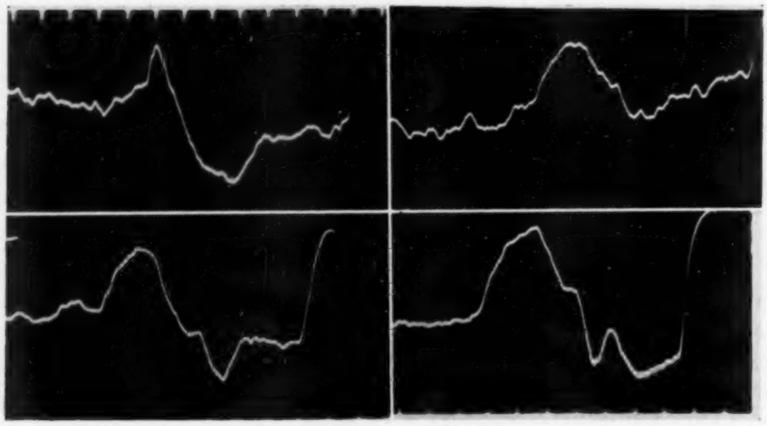


Fig. 4.—Mitral P waves.

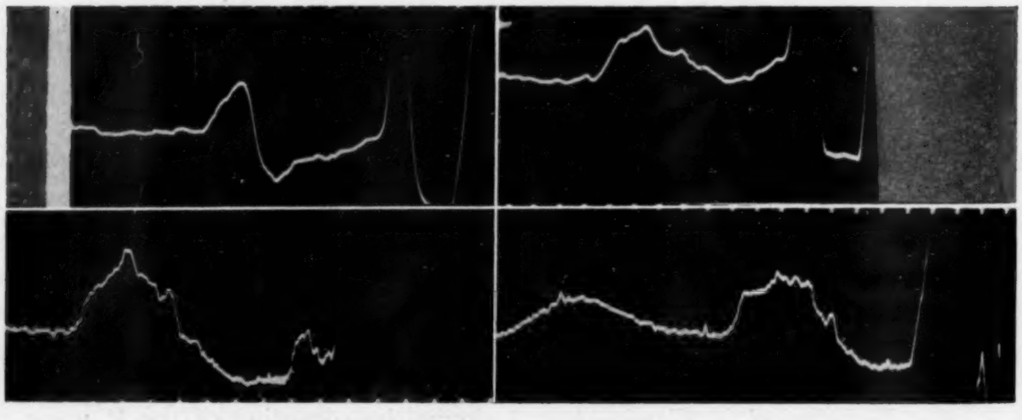


Fig. 5.—Pulmonary P waves with S-T_a well under base line.

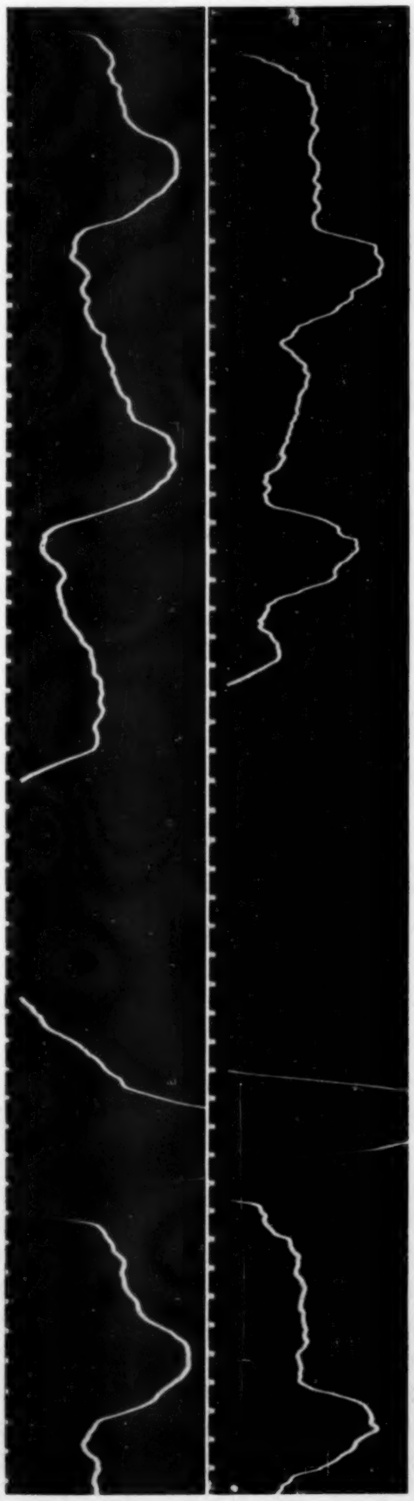


Fig. 6.—Auricular flutter.

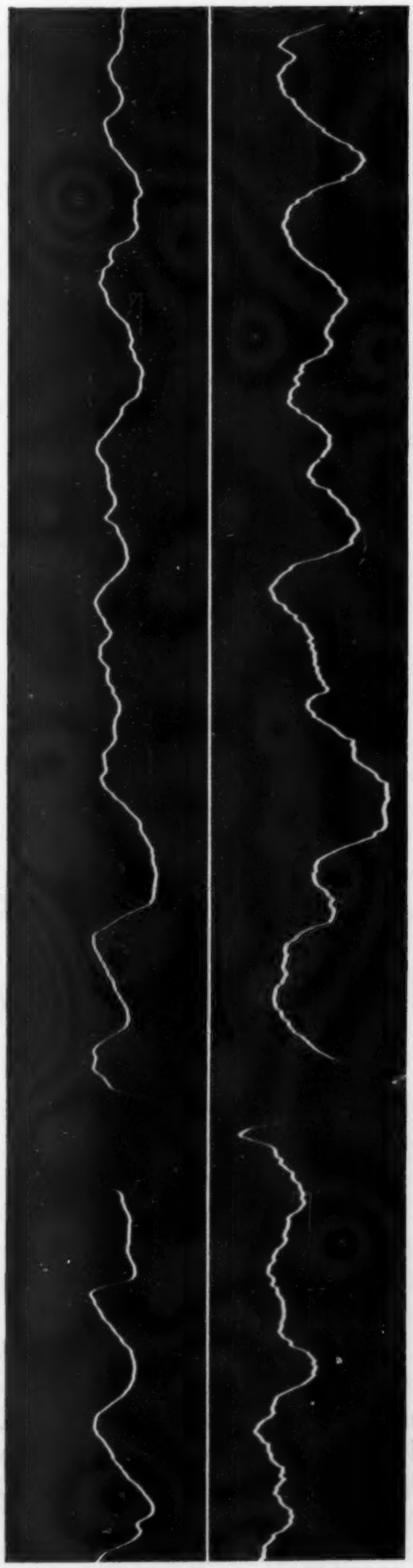


Fig. 7.—Auricular fibrillation.

wave of the RS kind, but also the existence of an auricular T wave, the presence of which has already been proved by others. In the account that comes next, we shall call S-T $_a$ segment (S-T$_p$) the portion of the auricular segment S-T which is the only visible part of our recordings and partly corresponds to what is generally called P-R segment.

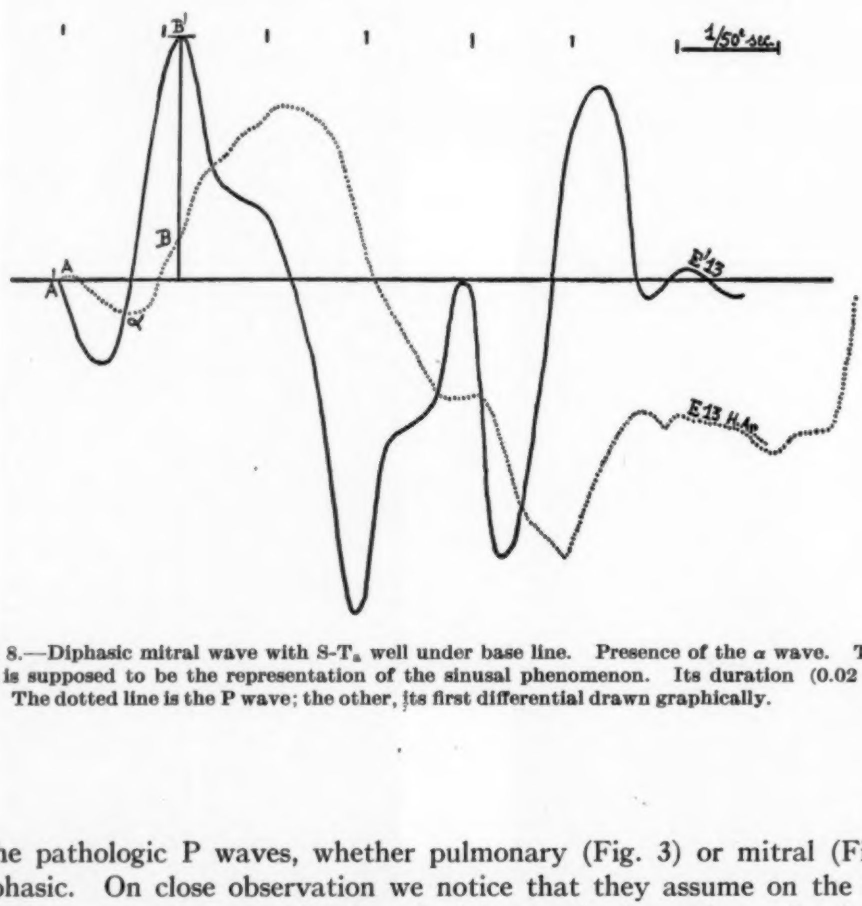


Fig. 8.—Diphasic mitral wave with S-T$_a$ well under base line. Presence of the α wave. The *AB* segment is supposed to be the representation of the sinusal phenomenon. Its duration (0.02 sec.) is normal. The dotted line is the P wave; the other, its first differential drawn graphically.

The pathologic P waves, whether pulmonary (Fig. 3) or mitral (Fig. 4), are diphasic. On close observation we notice that they assume on the whole the well-known aspect generally described in standard treatises. In the case of the mitral P wave, however, and in most cases of that type, a small negative wave (wave α) appears at the beginning of the P wave in lead E13. More will be said about it later. Then, we desire to draw attention to what is called by us the displacement of S-T $_a$ described for the first time to our knowledge in the theses of two of us.[1,2] In analogy of what goes on in the case of the ventricular complex, it has seemed to us, after a close study of fifty observations, whether pulmonary or mitral and mitro-aortic, that the displacement of S-T $_a$, real and notable, had a pathologic value, since the clinical state often revealed in such cases patent signs of myocardic failure (Figs. 4 and 5). At last we consider it of interest to give a recording of a flutter (Fig. 6) and a fibrillation (Fig. 7) as obtained by our method.

ANALYSIS OF P

A convenient means of analyzing a given curve is the study of the derived function of that curve. It is a fact that, great as the amplifications of P can be, it has always been impossible for us clearly to establish the sinusal phenomenon, the duration of which has been held by classical authors to be very short, ranging from 0.01 to 0.02 sec. and therefore most likely intermingled with P itself at its very beginning. So, we were led to draw graphically the first differential function of our normal and pathologic curves. As can be inferred from the aspect of P, the derived function shows at its beginning a maximum which, in normal curves, takes place between 0.01 and 0.02 sec., that is within the usual limits of time of the sinusal phenomenon. As a convenient hypothesis we have therefore admitted that segment AB, as shown in Fig. 8, represented the wave or the sinusal phenomenon. In these conditions, Fig. 9 shows an abnormal segment AB, since its duration is equal to 0.04 sec. In all likelihood,

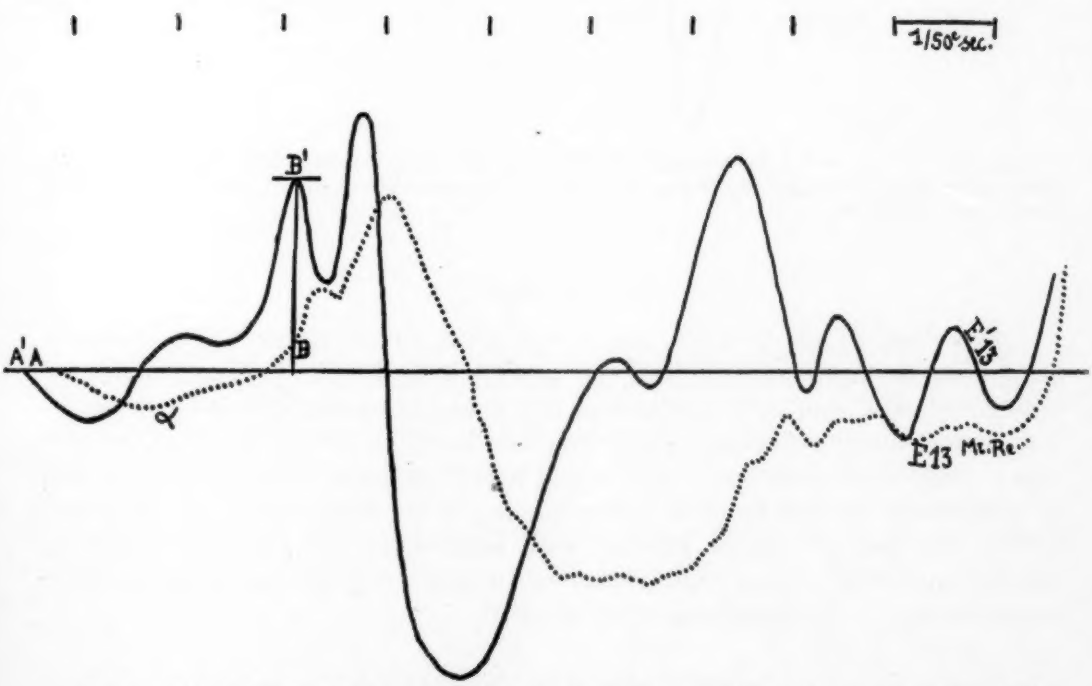


Fig. 9.—Diphasic mitral P wave with S-T_a level. *AB* **is supposed to be representation of the sinusal phenomenon. It is abnormally stretched. Its duration exceeds 0.04 sec. Presence of the α wave.**

we must be dealing here with a real incomplete sinoauricular dissociation. We feel all the more inclined to adopt that interpretation because the case is that of a mitral P wave in a 12-year-old girl undoubtedly suffering from rheumatic heart disease. Moreover, we have been lucky enough to record a partial sinoauricular block of Type 3 in a 74-year-old female patient suffering from athero-

matosis. Fig. 10 shows the P wave appearing after a complete silence equal to five P-P intervals. The drawing of the derived function of that P wave seems to reveal a sinusal phenomenon lasting 0.04 sec. and therefore abnormal.

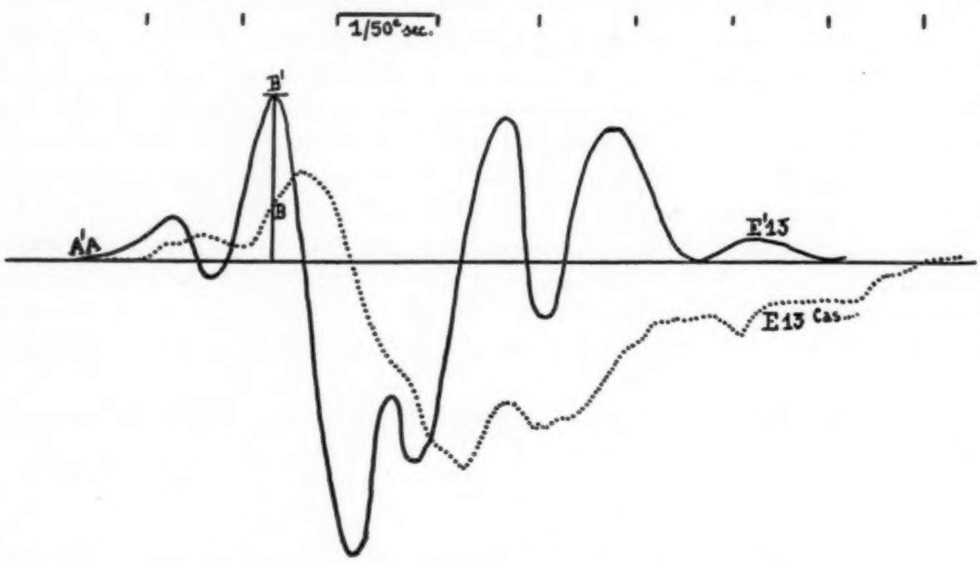


Fig. 10.—P wave of the diphasic sinoauricular block and its first differential. The *AB* segment, which is supposed to represent the sinusal phenomenon, is abnormally stretched, and its duration is nearly equal to 0.04 sec.

CONCLUSIONS

The study of the P wave, due to the great amplification, has been made easy using the apparatus devised and perfected by Bladier. The tracings we have obtained through the medium of this apparatus make it possible to interpret a great many atriograms which would be hardly legible in the usual recordings. Besides the pulmonary and mitral hearts we have thus examined it will be possible to use this method in like manner in the examination of congenital hearts and that of auricles affected with infarction. We are now perfecting the recording of the P wave and its derived function, and testing, through numerous experiments, the hypothesis we have raised.

CONCLUSIONES IN INTERLINGUA

Le apparato ideate e perfectionate per Bladier ha, gratias a su grande amplification, multo facilitate le studio del unda P. Le traciamentos que nos ha obtenite per medio de iste apparato permitte le interpretation de multe atriogrammas que in le registrationes customari esserea a pena legibile. Per iste methodo nos ha examinate cordes con anormalitates pulmonal e mitral. Il esserea etiam possibile applicar le mesme methodo al examine de cordes con defectos congenite e de auriculas infarcite. Nos nunc labora a perfectionar le registration del unda P e de su function derivate, e a probar per numerose experimentos le hypothese que nos ha proponite.

REFERENCES

1. Colombani, F. X.: Thèse, Marseille, November, 1953.
2. Bonifaci, J.: Thèse, Marseille, January, 1954.
3. Bladier, B.: Etude d'un electrocardiogramme fidèle et mise en evidence de la complexité de l'onde auriculaire P, Centre de Recherches Scientifiques, industrielles, maritimes. Note 123, April 1947.
4. Bladier, B. and Bonnet, M.: Electrocardiographie, Etude de l'onde P, C.R.S.I.M. Note 173, June, 1948.
5. Bladier, B.: Etude de l'impulsion auriculaire P, en fonction de l'effort. C.R.S.I.M. Note Vectocardiographie de, 303, December, 1951.
6. Bladier, B.: Vectocardiographie de l'onde P, Resultats obtenus C.R.S.I.M. Note 184, November, 1948.
7. Bonnet, M. and Bladier, B.: Polyphasisme de l'onde P, en derivation precordiale F avec un appareillage specialement construit pour l'etude electrique de l'oreillette, Arch. mal. coeur **12**:752, 1948.
8. Pruche, A.: Etude du complexe auriculaire de l'electrocardiogramme sous grande amplification, Arch. mal. coeur **12**:410, 1948.
9. Rijlant, P.: L'oscillographe cathodique du coeur de l'homme C.R. Soc. Biol. **1**:42, 1932; Essai d'interpretation des ondes de l'oscillographe cathodique du coeur de l'homme. C.R. Soc. Biol. **3**:933, 1933.
10. Meyer-Heine, A.: Electrocardiogramme et oscillation de relaxation, Semaine hôp. Paris **23**:269, 1947.
11. Jammet, J.: Essai d'analyse physico-mathematique des electrocardiogrammes, Semaine hôp. Paris **23**:257, 1947.

A STUDY OF THE ELECTROCARDIOGRAM AND VECTORCARDIOGRAM IN CONGENITAL HEART DISEASE

II. Vectorcardiographic Criteria for Ventricular Hypertrophy

Ephraim Donoso, M.D.,* Samuel O. Sapin, M.D.,
Eugene Braunwald, M.D.,** and
Arthur Grishman, M.D.

New York, N. Y.

INTRODUCTION

The differential diagnosis of congenital cardiac malformations requires accurate determination of the type of ventricular hypertrophy present. The initial phase of this study of the electrocardiogram and vectorcardiogram in congenital heart disease consisted of an analysis of the electrocardiogram in patients with congenital heart disease and unilateral ventricular hypertrophy.[1] It is the purpose of this communication to analyze the vectorcardiograms in the same patients and to compare the vectorcardiographic with the electrocardiographic findings. In this manner, it is hoped to establish the relative clinical merits of these techniques in the determination of ventricular hypertrophy.

There have been several previously published reports of the vectorcardiogram in congenital heart disease.[2-11] However, these earlier studies were based on relatively limited clinical material.

MATERIAL AND METHODS

The 135 patients selected for this study had congenital cardiac lesions which appeared to be well-established by a combination of post-mortem, surgical, and laboratory methods, including cardiac catheterization and angiocardiography, previously described in detail.[1] Patients with lesions producing an increased burden on only one ventricle were considered to have unilateral hypertrophy of that ventricle.

There were sixty-six patients with unilateral right ventricular hypertrophy

From the Departments of Medicine and Pediatrics and the Cardiographic Department, The Mount Sinai Hospital, New York, N. Y.

Presented in part at the Second World Congress of Cardiology and the 27th Annual Scientific Session of the American Heart Association, Inc., Sept. 12-17, 1954, Washington, D. C.

Received for publication March 9, 1955.

*Fellow, Dazian Foundation for Medical Research.

**Postdoctoral Research Fellow of The National Heart Institute, United States Public Health Service.

(tetralogy of Fallot, 26; pulmonic stenosis, 20; interatrial septal defect, 19; aberrant pulmonary veins, 1) and twenty-eight patients with unilateral left ventricular hypertrophy (aortic or subaortic stenosis, 12; coarctation of the aorta, 11; tricuspid atresia, 5). The third group of patients, to be analyzed in a subsequent report, had lesions which do not clearly produce unilateral ventricular hypertrophy.

Of the ninety-four patients with unilateral ventricular hypertrophy to be discussed here, about one-half were under 10 years of age, and only one was less than 1 year of age. The diagnoses and ages of these patients have been analyzed in detail.[1]

The electrocardiograms were recorded on a Technicon three channel direct-writing cardiograph at a paper speed of 50 or 100 mm./sec. and occasionally at 25 mm./sec., at one-half normal, normal, and one and one-half times normal standardization. In addition to the 12 conventional leads, vector component leads A,B, and C were obtained in all, and right precordial leads in many of the patients.

As discussed in detail in the first communication of this series,[1] we believe that the most reliable criteria for the electrocardiographic diagnosis of right ventricular hypertrophy can be obtained from electrocardiographic measurements in a large series of normal subjects.[12] When these normal limits of voltage or ventricular activation time are exceeded, the electrocardiographic diagnosis of ventricular hypertrophy may be reliably established in the absence of conduction disturbances, an RSR′ pattern in right precordial leads, or myocardial infarction. The specific criteria employed in the electrocardiographic diagnosis of ventricular hypertrophy were listed previously.[1] The electrocardiographic diagnoses of incomplete and complete right bundle branch block were established according to the criteria of Wilson and associates[13] and Barker and Valencia.[14] Electrocardiograms presenting an RSR′ pattern in the right precordial leads with a QRS duration of 0.08 to 0.11 sec. were diagnosed as incomplete right bundle branch block, while those with a QRS duration of 0.12 sec. or more as complete right bundle branch block. We have termed the electrocardiographic pattern of an RSR′ in right precordial leads with a QRS duration of 0.07 sec. or less, the "RSR′ pattern."

The vectorcardiograms were obtained using the cube method of electrode placement, based on a modification of the Duchosal-Sulzer orthogonal arrangement for the placement of the electrodes,[15,16] employing a triple, or a special single Technicon vector oscilloscope. The vector loop was interrupted 400 times per second by intensity modulations, permitting time analysis of the loop. The interrupted lines were wedge-shaped with the wider end leading, thus permitting accurate and simple interpretation of the direction of inscription. The polarity and lead arrangements used were described previously.[16]

Positivity is directed anteriorly and downward and to the left (observer's right) in the three planes. The horizontal (H), sagittal (S), and frontal (F) plane projections of the spatial vector appear in all illustrations, in this order, reading from left to right.

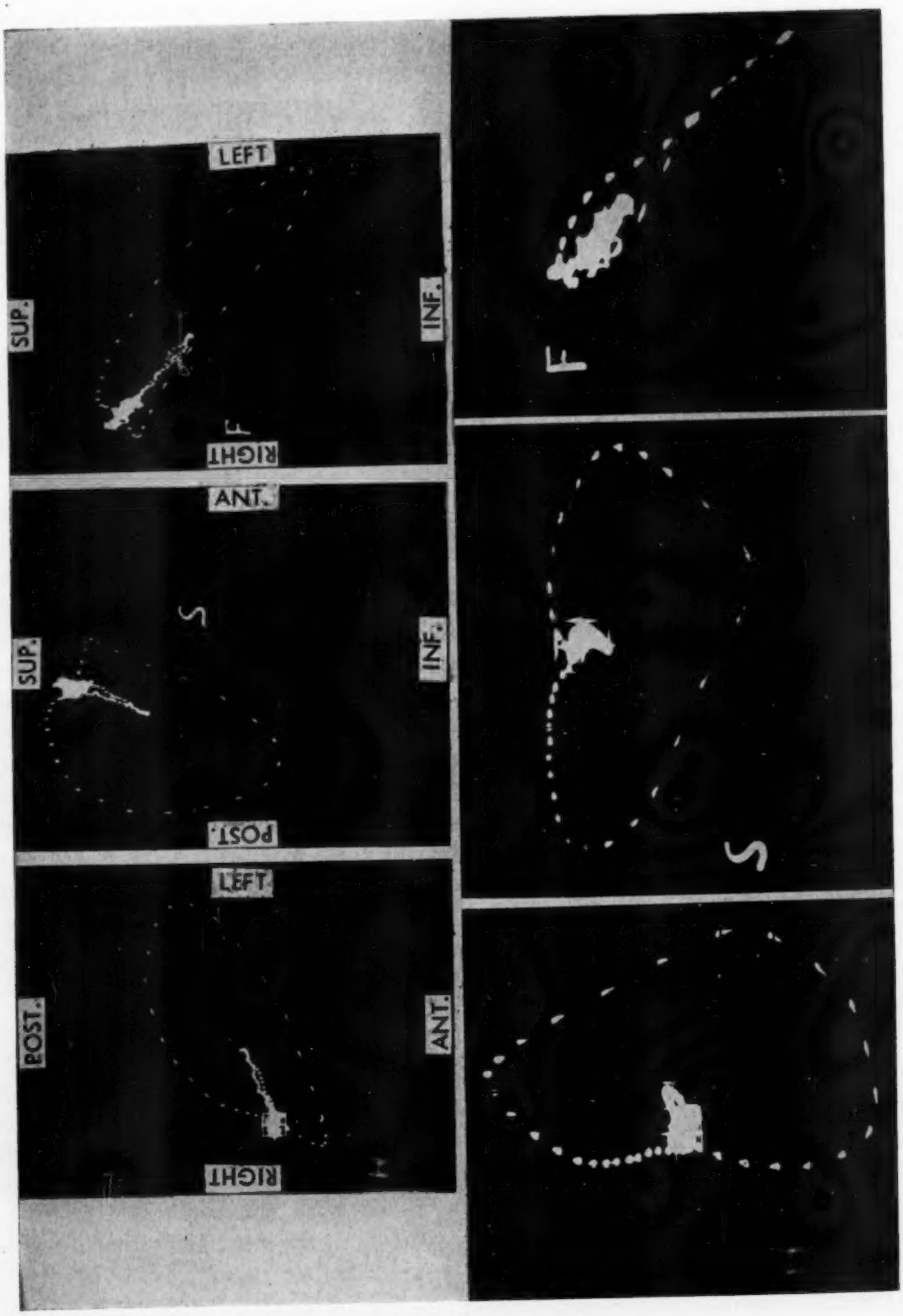


Fig. 1.—Spatial vectorcardiogram in normal adult (upper tracing) and normal child (lower tracing).

RESULTS

1. *Right Ventricular Hypertrophy.*—The spatial vectorcardiograms in the sixty-six patients with lesions producing unilateral right ventricular hypertrophy were divided into four separate groups on the basis of the appearance of the vectorcardiographic patterns. Subsequently, the clinical pictures and electrocardiographic patterns of the patients comprising each group were analyzed.

The normal spatial vectorcardiogram obtained by the cube reference system, as described by Scherlis and associates[17] (Fig. 1), is oriented to the patient's left, inferiorly, and somewhat posteriorly. In the horizontal plane, the normal QRS vector loop exhibits an initial small deflection anteriorly and to the right. The loop then proceeds in a counterclockwise direction to the left and finally slightly posteriorly. In normal children, the QRS loop differs in that it is situated more anteriorly[18] (Fig. 1).

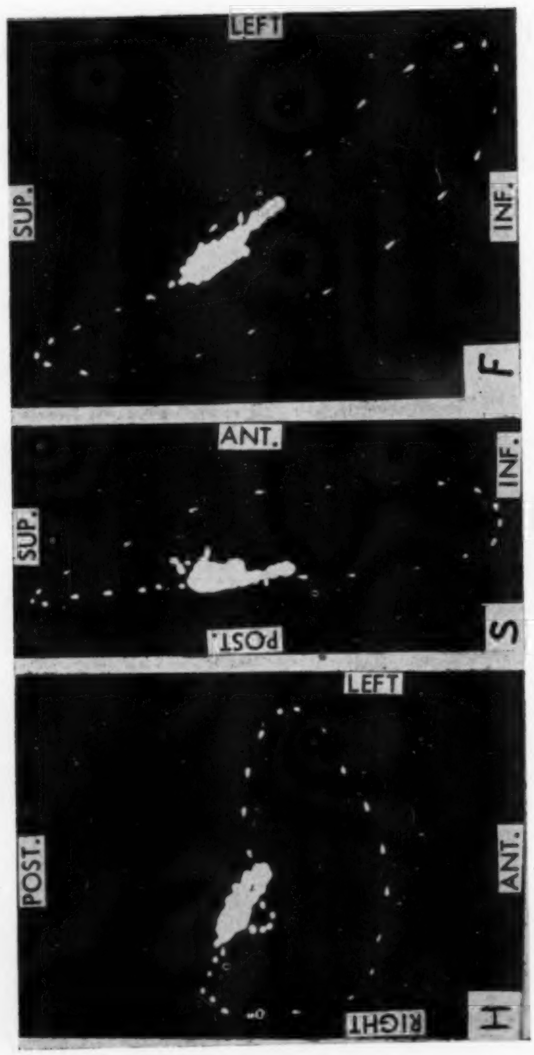
Group 1: The QRS loop is, in these cases, oriented mainly inferiorly and anteriorly. The horizontal projection is characterized by an initial, small deflection directed to the right and anteriorly, followed by a larger deflection to the left and somewhat posteriorly. The loop then turns sharply to the right and anteriorly again, with a clockwise return to the point of origin (Fig. 2). The electrocardiogram theoretically derived from such a vectorcardiographic pattern presents an RSR′ in right precordial leads (Fig. 2). In all eight patients in this group, the electrocardiograms actually revealed such an RSR′ pattern.

There were three patients with pulmonic stenosis and five patients with interatrial septal defect in this group. The systolic right ventricular pressures and electrocardiographic diagnoses in these patients are indicated in Table I.

TABLE I. ANALYSIS OF DIAGNOSES, RIGHT VENTRICULAR SYSTOLIC PRESSURES AND ELECTROCARDIOGRAMS IN EIGHT PATIENTS WITH THE GROUP I VECTORCARDIOGRAPHIC PATTERN OF RIGHT VENTRICULAR HYPERTROPHY

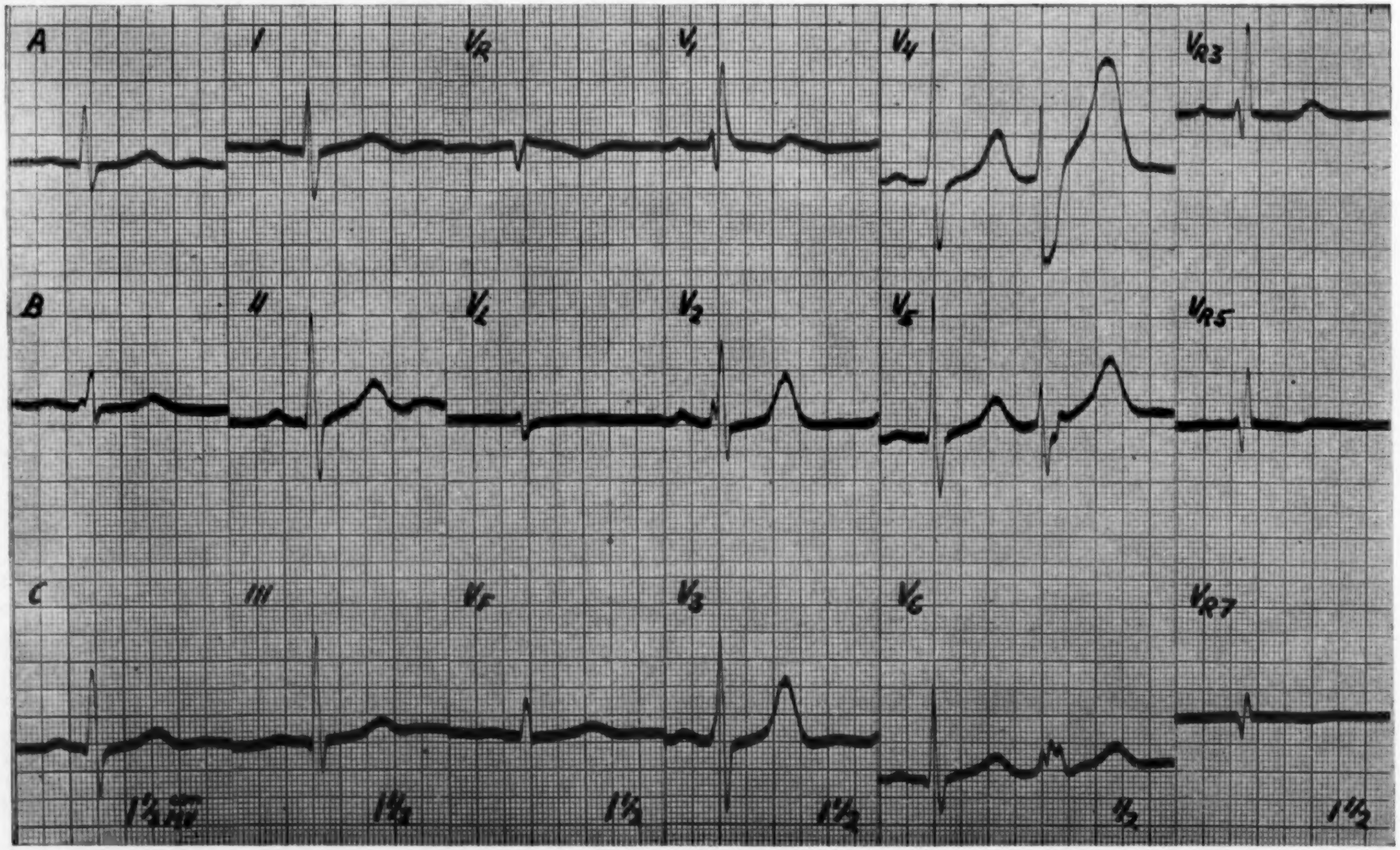
DIAGNOSIS	NO. OF PATIENTS	RIGHT VENTRICULAR SYSTOLIC PRESSURE (MM. HG)		ELECTROCARDIOGRAMS	
		RANGE	AVERAGE	INC. RBBB	"RSR′ PATTERN"
Pulmonic stenosis	3	60-96	83	2	1
Interatrial septal defect	5	30-46	35	4	1
Totals	8			6	2

Group 2: The QRS loop of the vectorcardiogram in this group is oriented more to the right than is Group 1. It is variable in that it may be directed inferiorly or superiorly, and either anteriorly or posteriorly. The direction of inscription of the loop in the horizontal plane is again clockwise. Since the portion of the loop immediately following the initial deflection is directed more anteriorly than in the vectorcardiograms in Group 1, one would expect to see



A.

Fig. 2, A. (For legend see opposite page.)



B.

Fig. 2.—A 16-year-old girl with pulmonic stenosis and a right ventricular systolic pressure of 100 mm. Hg. The vectorcardiogram (*A*) shows right ventricular hypertrophy (Group 1), while the electrocardiogram (*B*) presents an RSR′ pattern in Lead V_1.

fewer patients in this group with an RSR′ in right precordial leads of the electrocardiogram. This is borne out by our findings of an RSR′ in right-sided chest leads in only five of the fifty-one patients with a Group 2 vectorcardiogram.

In Table II, the diagnoses, right ventricular systolic pressures, and electrocardiographic diagnoses of the fifty-one patients in this group are presented.

TABLE II. ANALYSIS OF DIAGNOSES, RIGHT VENTRICULAR SYSTOLIC PRESSURES AND ELECTROCARDIOGRAMS IN FIFTY-ONE PATIENTS WITH THE GROUP 2 VECTORCARDIOGRAPHIC PATTERN OF RIGHT VENTRICULAR HYPERTROPHY

DIAGNOSIS	NO. OF PATIENTS	RIGHT VENTRICULAR SYSTOLIC PRESSURE (MM. HG)		ELECTROCARDIOGRAPHIC DIAGNOSIS				
		RANGE	AVERAGE	RVH	INC. RBBB	"RSR′"	COMP. RBBB	NORMAL
Tetralogy of Fallot	24	68-160	97	21		2		1
Pulmonic stenosis	16	48-200	100	9		1		6
Interatrial septal defect	10	30-90	60	7	1		1	1
Aberrant pulmonary veins	1			1				
Totals	51			38	1	3	1	8

The electrocardiograms in this group most frequently revealed prominent R waves over the right and prominent S waves over the left precordium. Slurring or notching of the upstroke of the large R waves was often observed (Fig. 3). This slurring or notching is due to the change in direction of the early portion of the vector loop. Occasionally, the ventricular complex in right-sided precordial leads presented a qR configuration; in such patients, the initial portion of the QRS loop proceeds immediately to the left.

When the QRS loop is oriented predominantly posteriorly and to the right, the precordial leads from V_1 to V_6 are rS in configuration, and the correct electrocardiographic diagnosis may be difficult. The early small deflection to the left and anteriorly results in the small R waves in the precordial leads, while the S waves are related to the major portion of the QRS loop which is directed posteriorly and to the right.

Axis deviation in the electrocardiogram is related to the orientation of the vector loop in the frontal plane. If the QRS loop in the frontal projection is oriented inferiorly and to the right, right-axis deviation is present in the standard leads. However, when the QRS loop is situated superiorly and to the right in the frontal plane, one may find predominant S waves in the three standard leads, the so-called "concordant S" pattern.

Left-axis deviation in the electrocardiogram may occur in the presence of anatomic, electrocardiographic and vectorcardiographic evidence of right ventricular hypertrophy since the QRS loop is occasionally inscribed to the left and superiorly in the frontal plane.

It is apparent that the marked variations in the electrocardiographic patterns of the patients in Group 2 can thus be explained by the various orientations of the QRS loop.

Group 3: The vectorcardiograms of the three patients in this group are directed chiefly anteriorly and superiorly. They are all characterized, in the horizontal plane, by an initial portion which courses to the left. The loop then turns and advances to the right, producing a figure-of-eight configuration (Fig. 4).

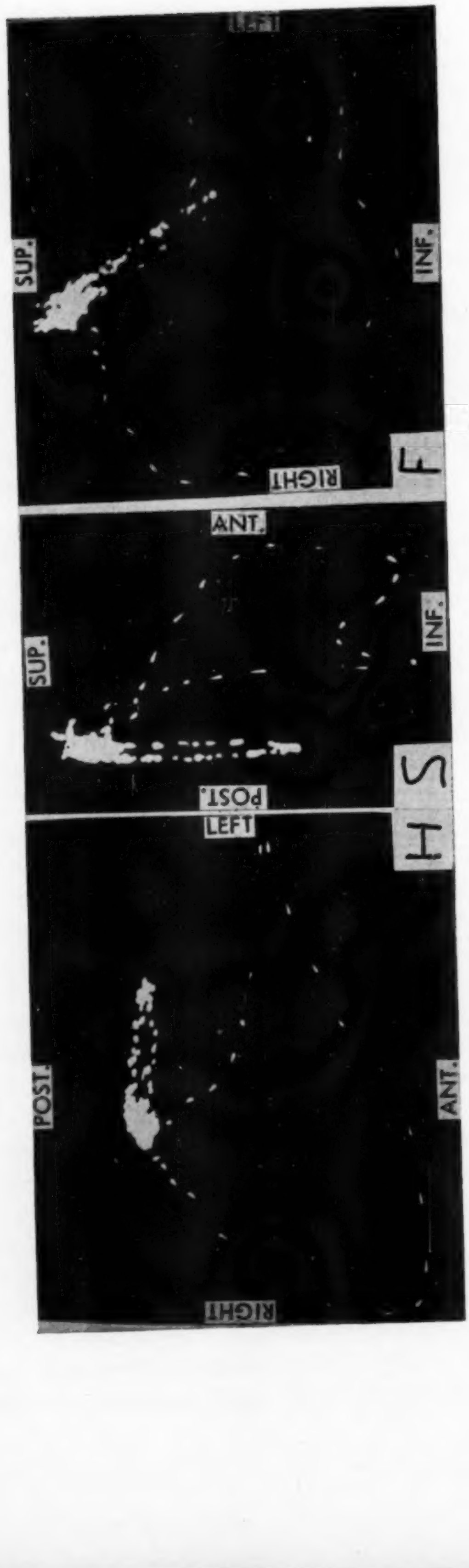
The first patient in this group had the tetralogy of Fallot (post-mortem confirmation), a systolic right ventricular pressure of 100 mm. Hg, and his electrocardiogram was interpreted as incomplete right bundle branch block. The other two patients in this group had interatrial septal defects, and the electrocardiograms were interpreted as normal in one (Fig. 4) and as right ventricular hypertrophy in the other.

Group 4: The vectorcardiograms in the four patients in this group do not reveal right ventricular hypertrophy although the latter was present anatomically.

One normal vectorcardiogram was obtained in a patient with tetralogy of Fallot (surgical confirmation). The electrocardiogram was similarly normal. Another patient with isolated pulmonic stenosis also had a normal vectorcardiogram; the electrocardiogram was interpreted as right ventricular hypertrophy and the systolic right ventricular pressure was 90 mm. Hg. A third patient with an interatrial septal defect had an unusual vectorcardiogram of a type not previously observed, and his electrocardiogram revealed right ventricular hypertrophy. The fourth patient, with an interatrial septal defect presented a vectorcardiographic pattern characteristic of right bundle branch block. The direction of inscription of the QRS loop in the transverse plane was counterclockwise, and in each projection the terminal portion was slurred, irregular in contour, and was directed to the right and anteriorly. The electrocardiogram of this patient was interpreted as incomplete right bundle branch block.

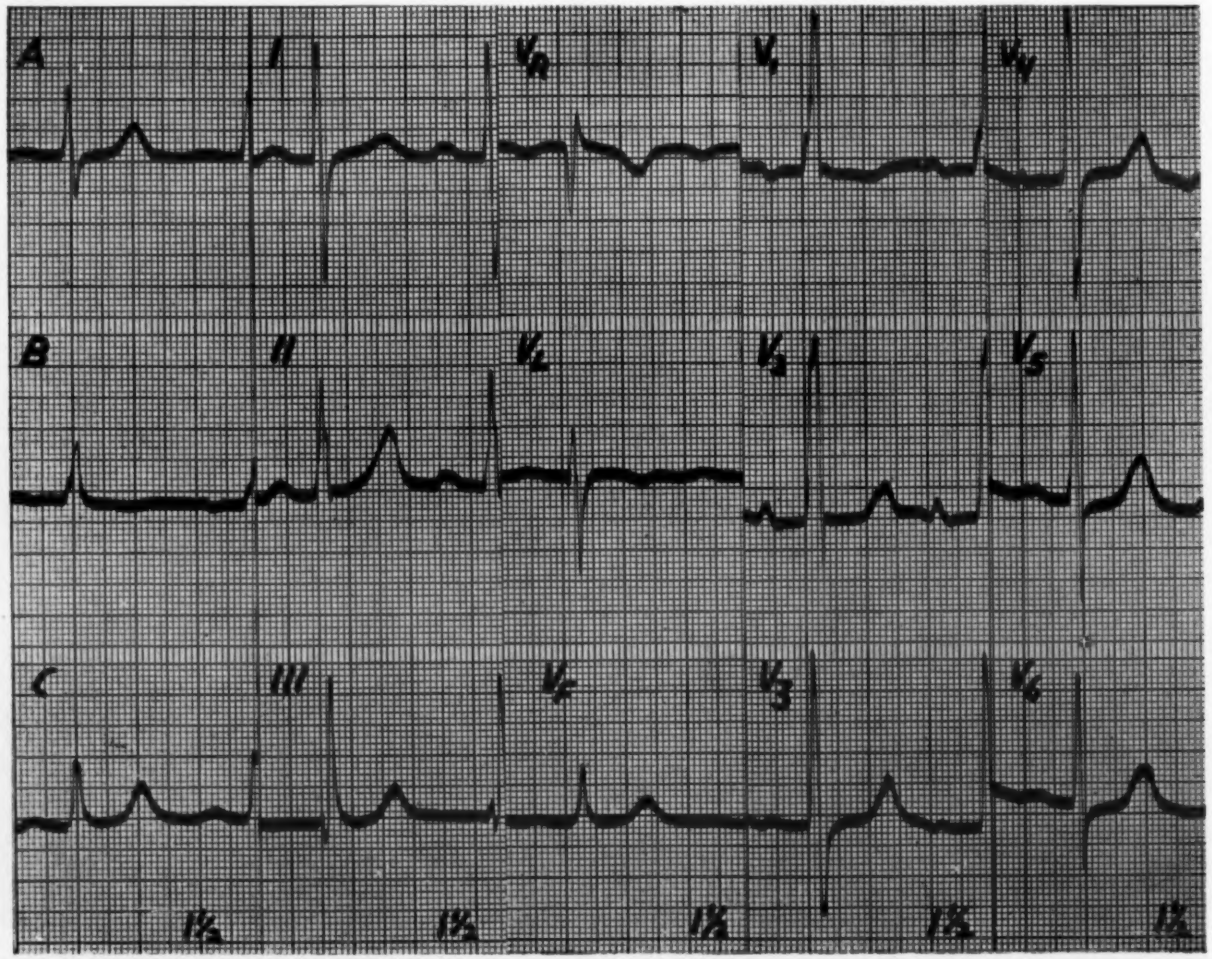
We have thus far omitted reference to the direction of inscription of the sagittal and frontal plane QRS loops of the vectorcardiogram. The normal QRS loop in the frontal plane may rotate in a clockwise or counterclockwise direction, and the mere direction of inscription in this plane would appear to have no diagnostic importance. In the sagittal plane, the normal direction of inscription is clockwise. Of the sixty-two patients comprising Groups 1, 2, and 3 (right ventricular hypertrophy vectorcardiograms) in the sagittal plane, nineteen had a clockwise inscribed loop, thirty-one a counterclockwise direction, and the remaining twelve had a figure-of-eight loop. No characteristic association of direction of inscription of the sagittal loop with any one group or lesion was apparent.

The normal T loop is oriented within a spatial angle of less than 30° to the long axis of the QRS loop. The orientation of the T loop was determined in two planes in each instance. The orientation of this loop was classified as either concordant (normal), discordant (opposite in orientation to the main axis of the QRS), or angular deviation (midway between concordant and discordant). Of the sixty-two patients with right ventricular hypertrophy in the vectorcardiogram, the T loops were concordant in eight, discordant in forty-five, and revealed angular deviation in nine. No consistent differences were noted in the T-loop orientation in each of the three right ventricular hypertrophy groups.



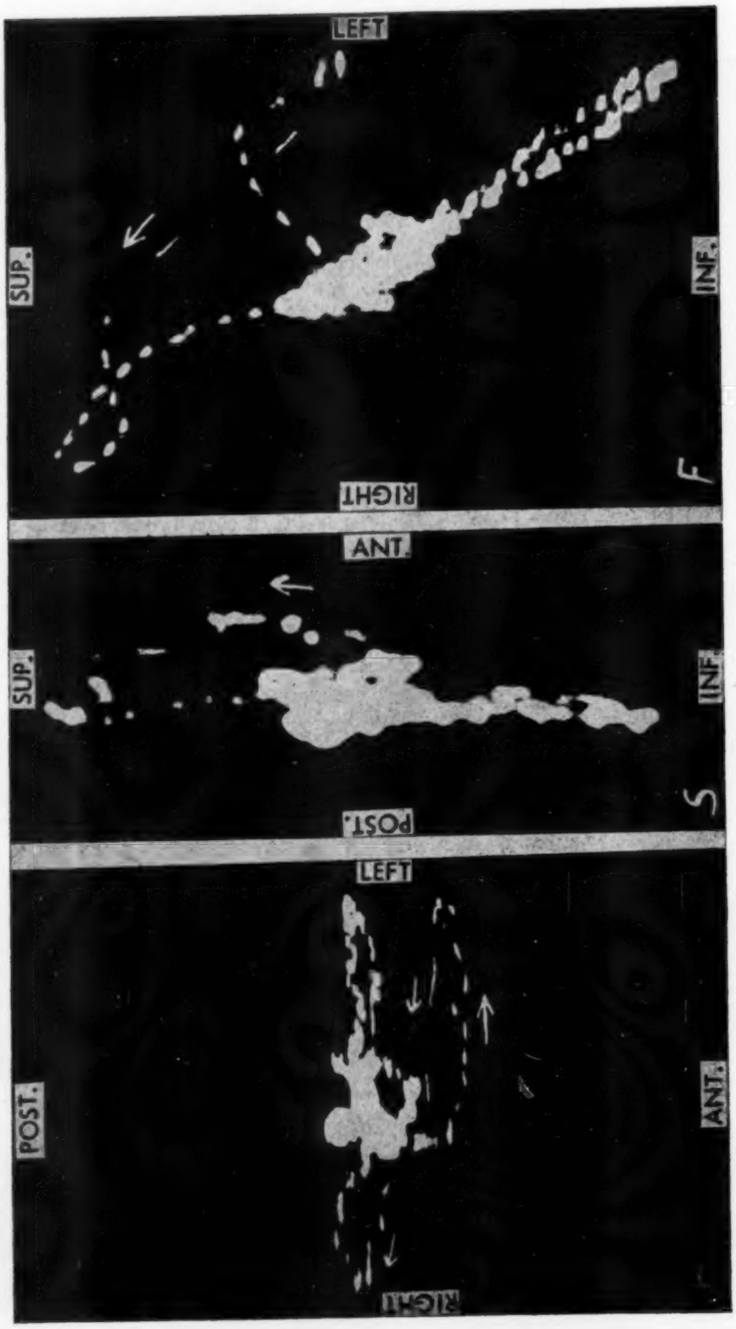
A:

Fig. 3, A. *(For legend see opposite page.)*



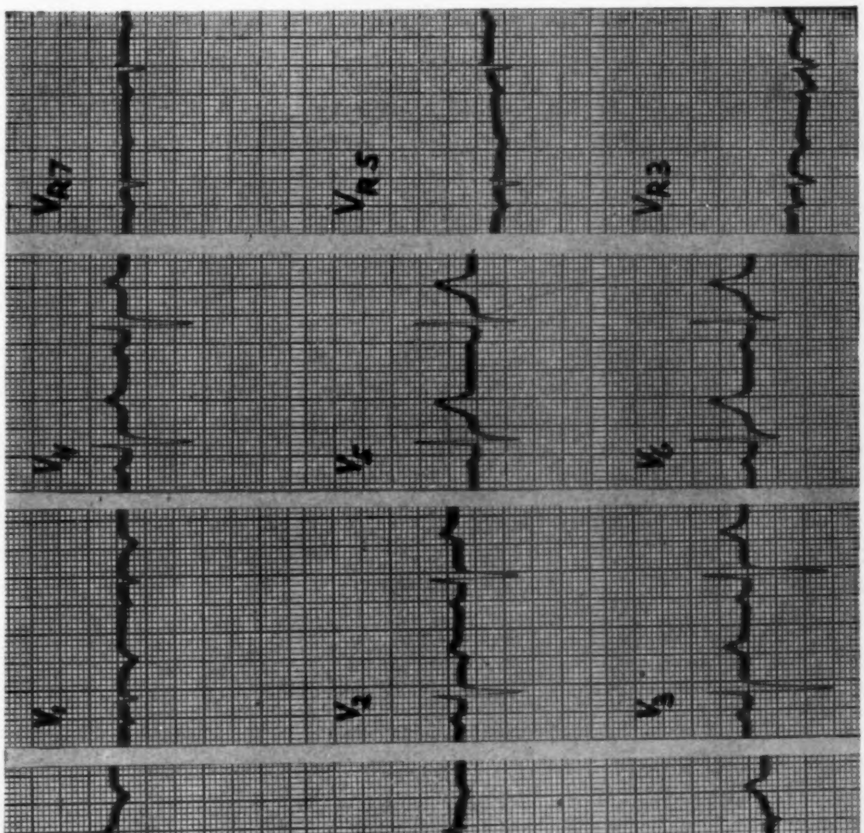
B.

Fig. 3.—A 4-year-old girl with the tetralogy of Fallot. The vectorcardiogram (*A*) shows right ventricular hypertrophy (Group 2), while the electrocardiogram (*B*) presents a slurred upstroke in Lead V_1.



A.

Fig. 4, A. (For legend see opposite page.)



B.

Fig. 4.—A 21-year-old female with interatrial septal defect. The vectorcardiogram (*A*) shows right ventricular hypertrophy (Group 3.) The electrocardiogram (*B*) is normal with left-axis deviation.

2. *Left Ventricular Hypertrophy.*—There was a total of twenty-eight patients with lesions producing left ventricular hypertrophy, and the vectorcardiograms may be conveniently divided into two groups.

Group 1: These patients had vectorcardiograms which we interpreted as indicating the presence of left ventricular hypertrophy.[19] In the presence of left ventricular hypertrophy, the QRS loop (Fig. 5) in the horizontal projection is characterized by an initial deflection anteriorly and somewhat to the right. The loop is then inscribed to the left and posteriorly in a counterclockwise direction. The long axis of the QRS loop is more posterior and superior than in the normal, and there is no appreciable alteration in the distances between time markings. The sagittal plane projection of the QRS loop is inscribed in a clockwise direction, and the loop is oriented more posteriorly than normal. The QRS loop in the frontal projection is generally oriented further to the left than in the normal and is usually inscribed in a counterclockwise direction. In this group, the T loop in each projection was discordant in thirteen of the sixteen cases. The QRS loop occasionally failed to close prior to the inscription of the T loop, resulting in an R-ST segment deviation in the scalar electrocardiogram. Table III shows the distribution of the sixteen patients in this group and their electrocardiographic diagnoses.

TABLE III. ANALYSIS OF DIAGNOSES AND ELECTROCARDIOGRAMS IN PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY AND GROUP 1 VECTORCARDIOGRAPHIC PATTERN (LEFT VENTRICULAR HYPERTROPHY)

DIAGNOSIS	NO. OF PATIENTS	ELECTROCARDIOGRAMS	
		NORMAL	LEFT VENTRICULAR HYPERTROPHY
Coarctation of the aorta	7	3	4
Subaortic or aortic stenosis	5	4	1
Tricuspid atresia	4	0	4
Totals	16	7	9

TABLE IV. ANALYSIS OF DIAGNOSES AND ELECTROCARDIOGRAMS IN PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY AND GROUP 2 VECTORCARDIOGRAPHIC PATTERN (NORMAL)

DIAGNOSIS	NO. OF PATIENTS	ELECTROCARDIOGRAMS	
		NORMAL	LEFT VENTRICULAR HYPERTROPHY
Coarctation of aorta	4	4	0
Subaortic or aortic stenosis	7	7	0
Tricuspid atresia	1	1	0
Totals	12	12	0

Group 2: The remaining twelve patients with lesions producing unilateral left ventricular hypertrophy had normal vectorcardiograms. Table IV presents the data from this group.

DISCUSSION

It should be emphasized that while the stated electrocardiographic and vectorcardiographic criteria may be applied to the diagnosis of ventricular hypertrophy due to all types of heart disease, the results presented here merely reflect their accuracy in congenital heart disease. Furthermore, this study is limited primarily to the postinfancy period, and the conclusions are not necessarily applicable to infants in the first few months of life.

Right Ventricular Hypertrophy.—In the initial report from this laboratory of the vectorcardiogram in right ventricular hypertrophy in congenital heart disease,[4] the vectorcardiographic patterns were divided into four types. After studying a considerably larger series of patients, it appears more satisfactory to alter this classification somewhat. These alterations are twofold.

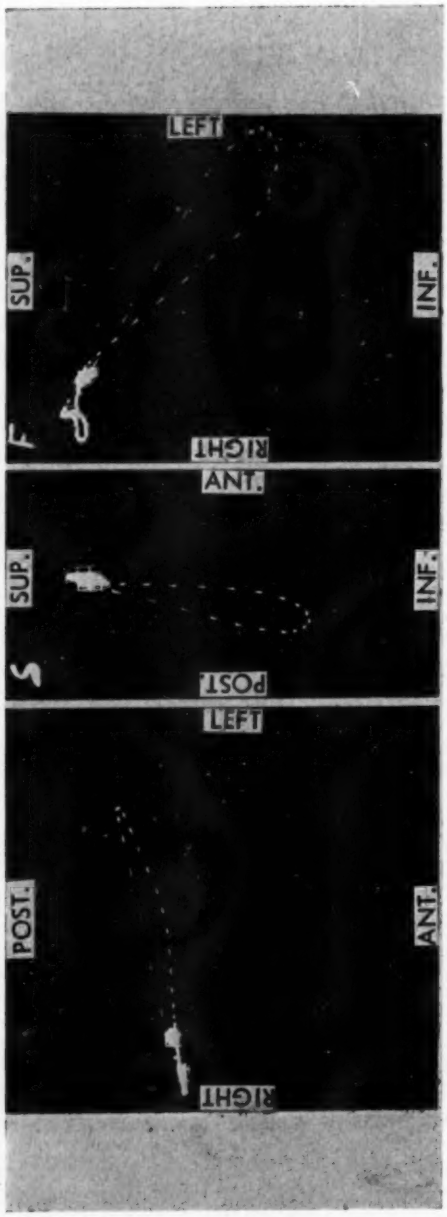
1. In the Group 2 of right ventricular hypertrophy described here, we include QRS loops which are directed posteriorly as well as anteriorly and superiorly as well as inferiorly. This represents a combination of two of the types described by Lasser and associates,[4] and was necessary because of such frequent overlapping of vectorial orientations as to make a division of little meaning.

2. We have now observed a total of four patients with lesions producing unilateral right ventricular hypertrophy who did not have the vectorcardiographic pattern of right ventricular hypertrophy. Two of these had normal vectorcardiograms, one had an unusual vectorcardiogram and the fourth had right bundle branch block. These form the present Group 4, not previously described.

Groups 1, 2 and 3 of this classification consist of vectorcardiograms which we interpret as indicating right ventricular hypertrophy. Wolff and co-workers[8] differ somewhat in their interpretation of these vectorcardiographic patterns which we believe indicate the presence only of right ventricular hypertrophy. These workers have stated that in the vectorcardiographic patterns of right ventricular hypertrophy, there are also signs of incomplete right bundle branch block. Hemodynamic data recently obtained in this laboratory furnishes strong evidence to support the interpretation that in most cases of right ventricular hypertrophy there is no evidence of conduction delay.[20]

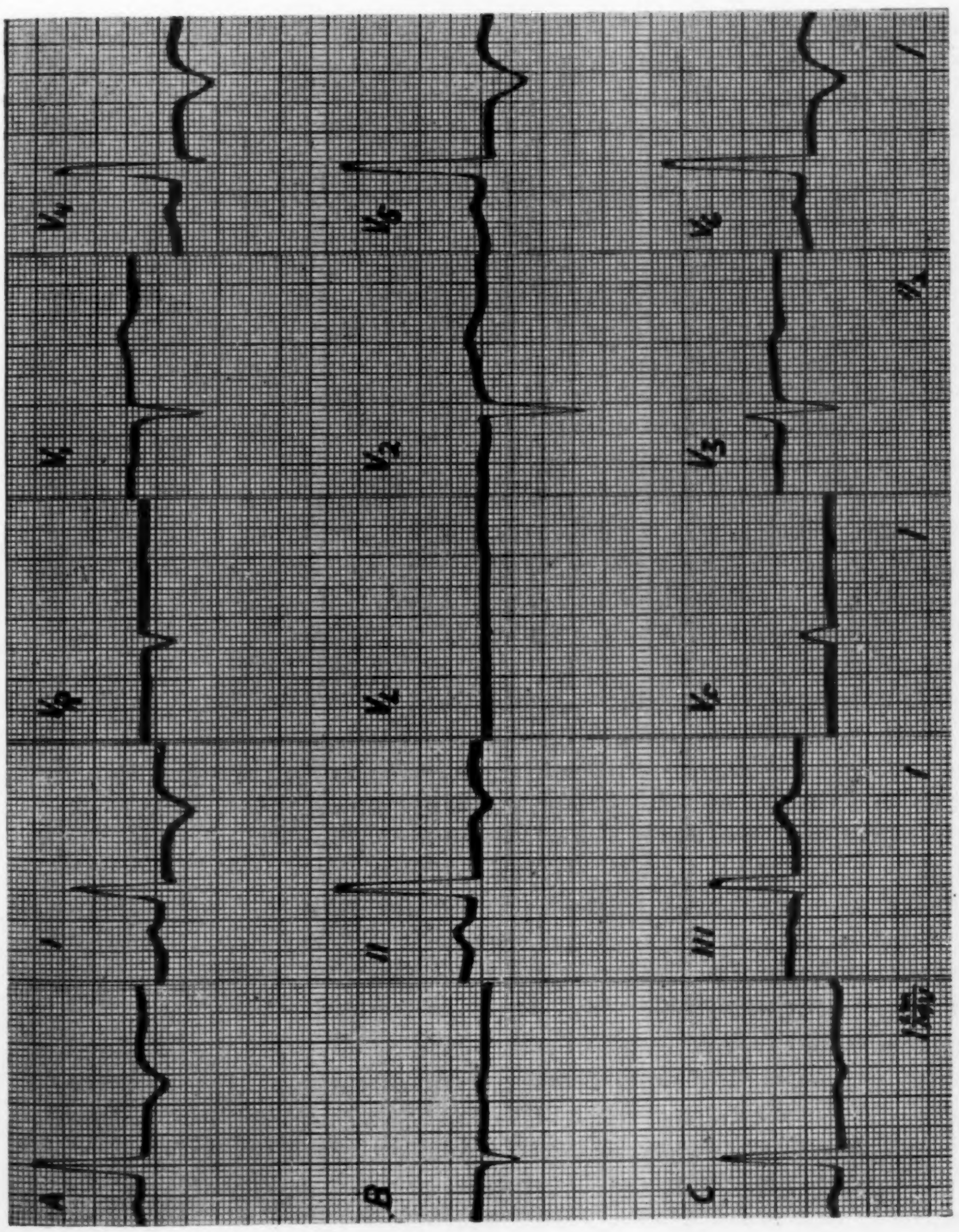
Analysis of the congenital lesions present in each group revealed that virtually all of the patients with tetralogy of Fallot were found to be in right ventricular hypertrophy Group 2. Although no explanation for this is apparent, if confirmed in a larger series of patients, this finding may prove to be of differential diagnostic value. The remaining patients with pulmonic stenosis and interatrial septal defect did not fall into as characteristic a grouping.

It appears from these studies that while the vectorcardiogram can accurately diagnose the presence of right ventricular hypertrophy, it offers limited information about the level of right ventricular pressure. The range and average



A.

Fig. 5, *A*. *(For legend see opposite page.)*



B.

Fig. 5.—A 16-year-old girl with congenital subaortic stenosis and coarctation of the aorta. The vectorcardiogram (*A*) shows left ventricular hypertrophy, and the electrocardiogram (*B*) presents left ventricular hypertrophy with no axis deviation.

of the right ventricular systolic pressures were highest in Group 2. However, since there was a significant degree of overlapping and the groups were not of comparable size, no absolute correlation could be established.

In a series of patients with right ventricular hypertrophy due to mitral stenosis and congenital heart disease, Elek and associates[9] found that with increasing degrees of right ventricular work, the vectorcardiographic orientation shifted progressively to the right. Further study is necessary to clarify the relation of the vectorcardiographic pattern to the degree of cardiac pressure, work, and anatomic hypertrophy.

Each of the four vectorcardiographic groups of right ventricular hypertrophy contained at least one patient with an RSR′ in the right precordial electrocardiographic leads. In addition, we have observed patients with normal hearts and normal vectorcardiograms in whom this electrocardiographic pattern was present. This again emphasizes that the RSR′ pattern in the electrocardiogram over the right precordium may reflect a variety of distinct entities which can be properly distinguished only by the vectorcardiogram.

In this series of sixty-six patients with congenital lesions producing right ventricular hypertrophy, fifteen presented the RSR′ pattern in right precordial electrocardiographic leads. Fourteen of these had vectorcardiographic patterns which we considered diagnostic of right ventricular hypertrophy, and the majority belonged to Group 1. The duration of the QRS complexes in these fourteen patients ranged from 0.07 sec. to 0.14 sec. The remaining case, a patient with an interatrial septal defect, had the vectorcardiographic pattern of right bundle branch block.

It is of interest with regard to this problem of the RSR′ complex that it has recently been reported[21-22] that following pulmonary valvulotomy in patients with pulmonic stenosis a change took place in the electrocardiogram in Lead V_1 from a tall R wave, characteristic of right ventricular hypertrophy, to an RSR′ pattern (diagnosed by standard electrocrdiographic criteria as incomplete right bundle-branch block). This lends further credence to our thesis that the RSR′, or so-called incomplete right bundle banch block pattern, in patients with anatomic right ventricular hypertrophy does not generally result from a conduction disturbance at all,[20] but rather is produced by the particular type of right ventricular hypertrophy vectorcardiographic loop described previously.

Left Ventricular Hypertrophy.—A rather marked difference in the frequency with which the vectorcardiogram detected right as opposed to left ventricular hypertrophy is apparent. Sixty-two of the sixty-six patients with lesions producing right ventricular hypertrophy had vectorcardiograms indicating this, while only sixteen of the twenty-eight patients with left ventricular hypertrophy had diagnostic vectorcardiograms. The frequency of normal vectorcardiograms in coarctation of the aorta and subaortic stenosis was not significantly different, but four of the five cases of tricuspid atresia were correctly diagnosed as having left ventricular hypertrophy (Tables III and IV).

One can only speculate as to the explanation for the relatively larger number of patients with normal vectorcardiograms in the left ventricular hypertrophy group. In the normal heart, beyond infancy, the balance of electrical forces

is influenced principally by the naturally preponderant left ventricle. A mild degree of left ventricular hypertrophy may not significantly affect this pre-existing normal left ventricular dominance, and therefore may not be detectable in the vectorcardiogram. As the hypertrophy of the left ventricle progresses, the QRS loop of the vectorcardiogram is often altered only slightly in its orientation (more posterior and superior) without any change in the direction of inscription. On the other hand, right ventricular hypertrophy is easily distinguished from the normal in the vectorcardiogram because it produces more drastic changes; there is an abnormal direction of the rotation as well as of the orientation of the vectorcardiogram.

Although it might be expected that more of the vectorcardiograms indicating left ventricular hypertrophy would be obtained in the older patients, there was no clear-cut evidence of this in our series.

Relative Merits of the Vectorcardiograms and Electrocardiogram in the Detection of Ventricular Hypertrophy.—

Right ventricular hypertrophy: In the initial report of this study,[1] we presented a set of electrocardiographic criteria for the diagnoses of right ventricular hypertrophy. These criteria, while strict enough to exclude false positive, proved to be diagnostic of right ventricular hypertrophy in forty-one of the fifty-one of our patients with lesions producing right ventricular hypertrophy and without an RSR′ in the right precordial leads. The vectorcardiographic criteria, on the other hand, could be applied to all sixty-six patients with right ventricular hypertrophy and were accurate in sixty-two of these.

Of the ten patients in whom electrocardiographic criteria could be applied but failed to detect right ventricular hypertrophy, the vectorcardiogram was diagnostic in eight. Furthermore, of the fifteen cases in which the electrocardiographic criteria could not be applied because of the presence of an RSR′ in right chest leads, fourteen were accurately diagnosed by the vectorcardiogram. Thus, the clinical superiority of the vectorcardiogram is clearly demonstrated.

In an experience with vectorcardiograms, in over 2,000 patients, not a single instance of the right ventricular hypertrophy vectorcardiographic pattern in a normal heart has been encountered. We feel that the finding of this pattern is diagnostic. The vectorcardiogram will occasionally, however, fail to diagnose the presence of right ventricular hypertrophy (four out of sixty-six patients).

In the clinical application of these techniques, the vectorcardiogram is certainly more valuable than the electrocardiogram in the detection of right ventricular hypertrophy. The vectorcardiogram appears most useful in the following instances: (1) when the electrocardiogram presents an RSR′ pattern in right precordial leads, and therefore our electrocardiographic criteria cannot be applied; (2) when the electrocardiogram is normal according to the criteria employed and right ventricular hypertrophy is clinically suspected, and (3) when screening electrocardiographic criteria[1] suggest right ventricular hypertrophy, but the more rigid electrocardiographic criteria are not satisfied.

Left ventricular hypertrophy: The accuracy of both the electrocardiogram and the vectorcardiogram in the detection of left ventricular hypertrophy due

to congenital heart disease has been disappointing. By applying the electrocardiographic criteria, only nine of the twenty-eight patients with left ventricular hypertrophy were properly diagnosed. The vectorcardiogram detected sixteen of this group, thus offering a greater diagnostic yield.

SUMMARY AND CONCLUSIONS

1. The vectorcardiograms in 135 patients with congenital heart lesions, in whom the diagnosis was well-established, were analyzed. The findings in the ninety-four patients with unilateral right ventricular hypertrophy and left ventricular hypertrophy are presented.

2. The vectorcardiographic patterns in the sixty-six patients with right ventricular hypertrophy could be divided into four separate groups. Sixty-two of these patients, forming Groups 1, 2, and 3, had vectorcardiographic evidence of right ventricular hypertrophy, while the remaining four patients in Group 4 did not. The vectorcardiographic and electrocardiographic patterns in each group are analyzed.

3. Fifteen patients in the group with unilateral right ventricular hypertrophy had an RSR′ pattern in the right precordial leads of the electrocardiogram; fourteen of these had vectorcardiographic patterns of only right ventricular hypertrophy and the remaining patient had vectorcardiographic evidence of right bundle branch block.

4. (a) The relative merits of the electrocardiogram and vectorcardiogram in the diagnosis of right ventricular hypertrophy are compared. The vectorcardiogram is found to be definitely superior. The vectorcardiogram is of particular value in those patients with normal electrocardiograms in whom right ventricular hypertrophy is suspected, and in those with an RSR′ pattern in right precordial leads.

(b) The vectorcardiogram was diagnostic in only sixteen of the twenty-eight patients with unilateral left ventricular hypertrophy. The electrocardiogram, however, was of even less value in this group.

5. Vectorcardiography has been demonstrated to be superior to the electrocardiogram, in determining the type of unilateral ventricular hypertrophy in congenital heart disease.

SUMMARIO IN INTERLINGUA

Vecto cardiogrammas spatial obtenite per le methodo a electrodos in arrangiamento cubic esseva analysate pro 66 patientes con hypertrophia dexteroventricular unilateral e pro 28 patientes con hypertrophia sinistroventricular unilateral debite a congenite morbo del corde. Le vectocardiogrammas del patientes con hypertrophia dexteroventricular esseva dividite in quatro gruppos. In tres de iste gruppos, includente 62 del total de 66 patientes, le vectocardiogrammas indicava hypertrophia dexteroventricular. Inter le 28 patientes con hypertrophia sinistroventricular, 16 habeva vectocardiogrammas diagnostic. Esseva executate un comparation del meritos relative de electro- e vectocardiogrammas in le diagnose de hypertrophia ventricular. Resultava que le vecto-

cardiogramma es superior. Illo se monstrava specialmente utile in patientes con le configuration RSR′ in derivationes electrocardiographic dexteroprecordial e in patientes in qui le electrocardiogramma es normal ben que il existe le suspicion que illes ha hypertrophia dexteroventricular.

REFERENCES

1. Braunwald, E., Donoso, E., Sapin, S. O., and Grishman, A.: A Study of the Electrocardiogram and Vectorcardiogram in Congenital Heart Disease. I. Electrocardiographic Criteria for Ventricular Hypertrophy, Am. Heart J. (In press).
2. Lasser, R. P., Borun, E. R., and Grishman, A.: A Vectorcardiographic Analysis of the RSR′ Complex of the Unipolar Chest Lead Electrocardiogram. III, Am. Heart J. **41**:667, 1951.
3. Lasser, R. P., and Grishman, A.: Vectorcardiograms Obtained in Patients With Right Ventricular Hypertrophy Whose Electrocardiograms Display an Unusual Axis Deviation or Left Axis Deviation, Am. Heart J. **41**:901, 1951.
4. Lasser, R. P., Borun, E. R., and Grishman, A.: Spatial Vectorcardiography: Right Ventricular Hypertrophy as Seen in Congenital Heart Disease, Am. Heart J. **42**:370 1951.
5. Durand, M., Metianu, C., and Vlad, P.: Le vectogramme chez l'enfant normal et dans les cardiopathies congenitales, Premier Congres Mondial de Cardiologie **2**:265, 1952.
6. Wenger, R., and Wick, E.: Vektorcardiographische Untersuchungen bei angeborenen Anomalien des Herzens und des grossen Gefässe, Cardiologia **20**:1, 1952.
7. Deglaude, L., and Laurens, P.: Recherches vectographiques dans les cardiopathies congenitales, Semaine hôp. Paris. **50**:17, 1952.
8. Wolff, L., Richman, J. L., and Soffe, A. M.: Spatial Vectorcardiography: Review and Critique. New England J. Med. **248**:810, 851, 1953.
9. Elek, S. R., Allenstein, B. J., Griffith, G. C., Cosby, R. S., and Levinson, D. C.: A Correlation of the Spatial Vectorcardiogram With Right Ventricular Hypertrophy, Am. Heart J. **47**:369, 1954.
10. Fowler, N. O., and Helm, R. A.: The Spatial QRS Loop in Right Ventricular Hypertrophy With Special Reference to the Initial Component, Circulation **7**:573, 1953.
11. Gardiner, J. M., and Lowe, T. E.: The Spatial Vectorelectrocardiogram in Right Ventricular Hypertrophy, Australasian Ann. Med. **3**:18, 1954.
12. Kossmann, C. E.: The Normal Electrocardiogram, Circulation **8**:920, 1953.
13. Wilson, C. N., Rosenbaum, F. A., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram, Adv. Int. Med. **2**:1, 1947.
14. Barker, J. M., and Valencia, R.: The Precordial Electrocardiogram in Incomplete Right Bundle Branch Block, Am. Heart J. **38**:376, 1949.
15. Duchosal, P. W., and Sulzer, R.: La vectocardiographie, Basle, 1949, S. Karger.
16. Grishman, A., Borun, E. R., and Jaffe, H. L.: Spatial Vectorcardiography: Technique for the Simultaneous Recording of the Frontal, Sagittal and Horizontal Projections: I, Am. Heart J. **41**:483, 1951.
17. Scherlis, L., Lasser, R. P., and Grishman, A.: Spatial Vectorcardiography. The Normal Vectorcardiogram. VI, Am. Heart J. **42**:235, 1951.
18. Grishman, A., and Scherlis, L.: Spatial Vectorcardiography, Philadelphia, 1952, W. B. Saunders Company.
19. Scherlis, L., and Grishman, A.: Spatial Vectorcardiography: Left Bundle Branch Block and Left Ventricular Hypertrophy: II, Am. Heart J. **41**:494, 1951.
20. Grishman, A., Braunwald, B., Sapin, S. O., and Donoso, E.: Hemodynamic Vectorcardiographic, and Electrocardiographic Observations in Right Bundle Branch Block (In preparation).
21. Blount, S. G., McCord, M. C., Mueller, H., and Swan, H.: Isolated Valvular Pulmonic Stenosis. Clinical and Physiologic Response to Open Valvuloplasty, Circulation **10**:161, 1954.
22. Landtman, B.: Postoperative Changes in the Electrocardiogram in Congenital Heart Disease. I. Pure Pulmonary Stenosis, Circulation **10**:859, 1954.

THE NORMAL POTENTIAL VARIATIONS ON THE EXTREMITY, BACK, AND PRECORDIAL ELECTRODES WITH REFERENCE TO CENTRAL TERMINALS OF ZERO AND NONZERO POTENTIAL

Robert H. Bayley, M.D.

Oklahoma City, Okla.

When Wilson and associates[7] first described the currently standard method for recording unipolar precordial and extremity leads they were fully aware of the assumptions which must be accepted if the potential of the central terminal is to be regarded as constant or unaffected by the electromotive forces which produce the potential variations at the limb and precordial electrodes. They asserted that the potential variations at the precordium were large in comparison with any variations which might be expected to occur at the central terminal. Consequently, they held that precordial leads recorded by pairing the central terminal with the exploring electrode accurately displayed the potential variations of the latter.[1] The author is unaware of any evidence to the contrary. On the other hand, the potential variations at the extremity electrodes are of a small order of magnitude, and it is reasonable to suppose that the potential variations of the central terminal, when they exist, might appreciably alter the form of the true potential variations of the extremity electrodes to an extent which could be undesirable if these electrodes were incorporated into vectorcardiographic leads. An electrode placed at the level of P_3, two centimeters to the left of the spine, might also have its potential variations V_B influenced by potential variations of the central terminal. The extremity and back electrodes (R), (L), (F), and (B) have the important electrical property of being remote from the heart in an electrical sense[2] and are therefore worthy of consideration for use in vectorcardiographic leads. It is the purpose of this communication to present the electrocardiograms of three normal young adult subjects which illustrate the manner in which a weighted central terminal influences the true potential variations V_R, V_L, V_F, and V_B at the corresponding electrodes when the unweighted central terminal is at a constant or zero potential throughout the cardiac cycle, and to illustrate the manner in which the unweighted central terminal influences these potentials when the weighted terminal is at a constant or zero potential throughout the cardiac cycle.

From the Department of Internal Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

These investigations were supported by grants from the National Heart Institute of the National Institutes of Health, Public Health Service.

Received for publication March 14, 1955.

CONCERNING METHODS AND TERMINOLOGY

The three subjects which were chosen for discussion each required a central terminal of a different type in order that the terminal involved remain at a constant potential or equivalent zero throughout the cardiac cycle. Studies reported elsewhere[2-4] from this laboratory have shown that occasionally the standard (unweighted) central terminal may remain at zero potential throughout the cardiac cycle. However, a terminal in which the resistances r and l in the branches to the arm electrodes were made 2.6 times the resistance in the branch to the leg electrode is superior to the unweighted terminal and was found to remain at zero potential throughout the cardiac cycle in one-half of a small group of normal young adult subjects. The value 2.6 represents an average of weightings in a group of twenty-odd subjects. The potential of this terminal is denoted by V_{TW} or by V_{TW} (r = l = 2.6f). The potential of the unweighted terminal is denoted by V_T or by V_T (r = l = f). In only three of thirty-four subjects studied was it necessary to convert the 3-branch terminal into a 4-branch terminal in order to bring the terminal potential to zero throughout the cardiac cycle. This was accomplished by inserting a resistance h between the terminal and the back electrode (B). The potential of the weighted terminal with resistance values other than TW (r = l = 2.6f) is denoted by $V_{T\omega}$. The third subject required a zero-potential terminal of this type wherein the resistances in thousands of ohms were r = 15, l = 17, and f = h = 5.

DISCUSSION OF ELECTROCARDIOGRAMS

The electrocardiogram recorded from the first subject is shown in Fig. 1. Here the unweighted terminal is of potential $V_T = 0$. Consequently, the leads recorded with this terminal as a reference display the true potential variations V_R, V_L, V_F, and V_B of the extremity and back electrodes. Similar leads are shown using the terminal TW (r = l = 2.6f). This terminal is not zero for the subject under discussion, and its influence upon the true potentials is observed to be an increase of the variations at the arm electrodes and a decrease in the variations at the leg electrode. The lead $(V_{TW} - V_T) = V_{TW}$ shows the true potential variations of the weighted terminal. The maximum error on the weighted terminal is 0.15 millivolt and is due almost entirely to the vertical or $\vec{E}_y$ component of the heart's field. This component may be considered proportional to V_F for purposes of the present discussion.

Leads recorded from the second subject are shown in Figs. 2*A* and 2*B*. For this subject it is known that $V_{TW} = 0$ and that $V_T \neq 0$. A careful study of the precordial leads indicates that, except for minor differences in the P deflection, the form of the deflections is uninfluenced by the potential of the unweighted central terminal, and the experiment tends to confirm the assertion of Wilson and associates.[1] In Fig. 2*B* it appears that the error of the unweighted terminal of potential $V_T \neq 0$ reduces the variations on the electrodes (R) and (L) and increases the variations on electrode (F). The time-potential variations on electrode (B) appear larger than those recorded with the unweighted terminal.

The true potential variations of the unweighted terminal are shown by the lead ($V_T - V_{TW}$) = V_T. In the majority of leads of this kind the error on $V_T \neq 0$ is in the form of a QS deflection and the true variations on the (F) electrode consist essentially of an R deflection. In Fig. 2*B*, however, inspection

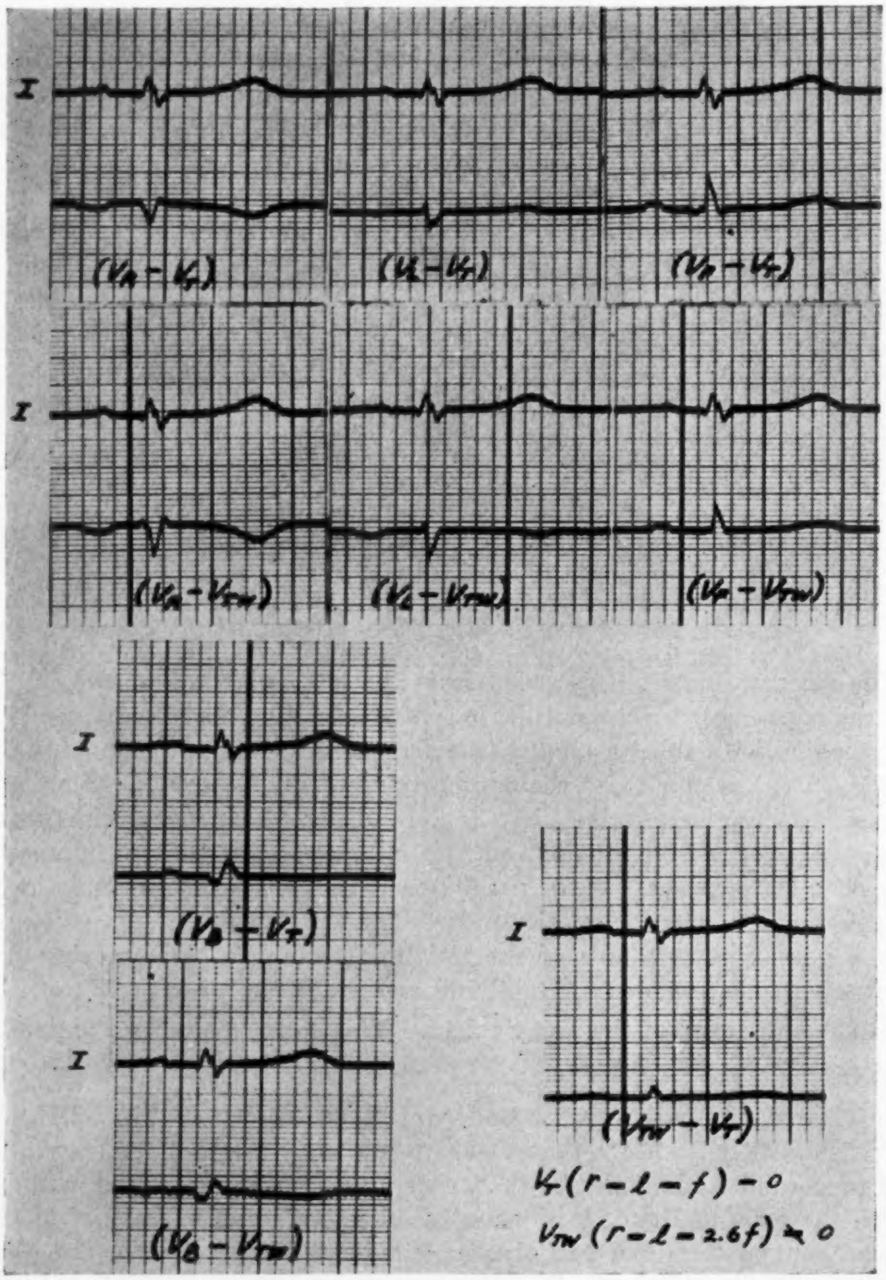


Fig. 1.—The true potential variations on the electrodes (R), (L), (F), and (B). In each instance Lead I is recorded simultaneously as a time reference. The influence of the terminal of potential $V_{TW} \neq 0$ is shown in the lower rows. The potential variations on the terminal of potential V_{TW} are shown in the lead ($V_{TW} - V_T$.)

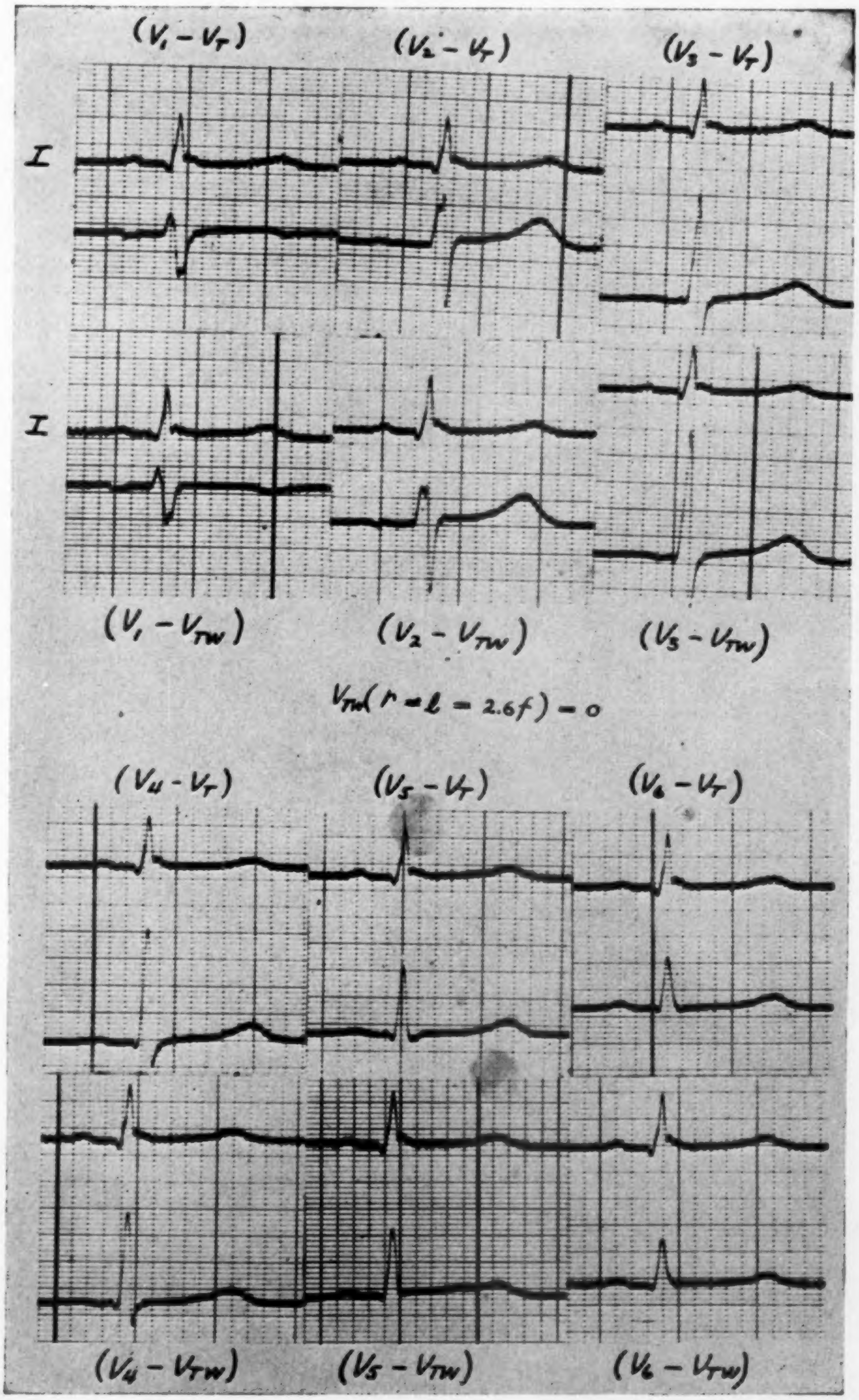


Fig. 2A.—Precordial potentials with respect to a zero terminal of potential V_{TW} and with respect to a nonzero terminal of potential V_T.

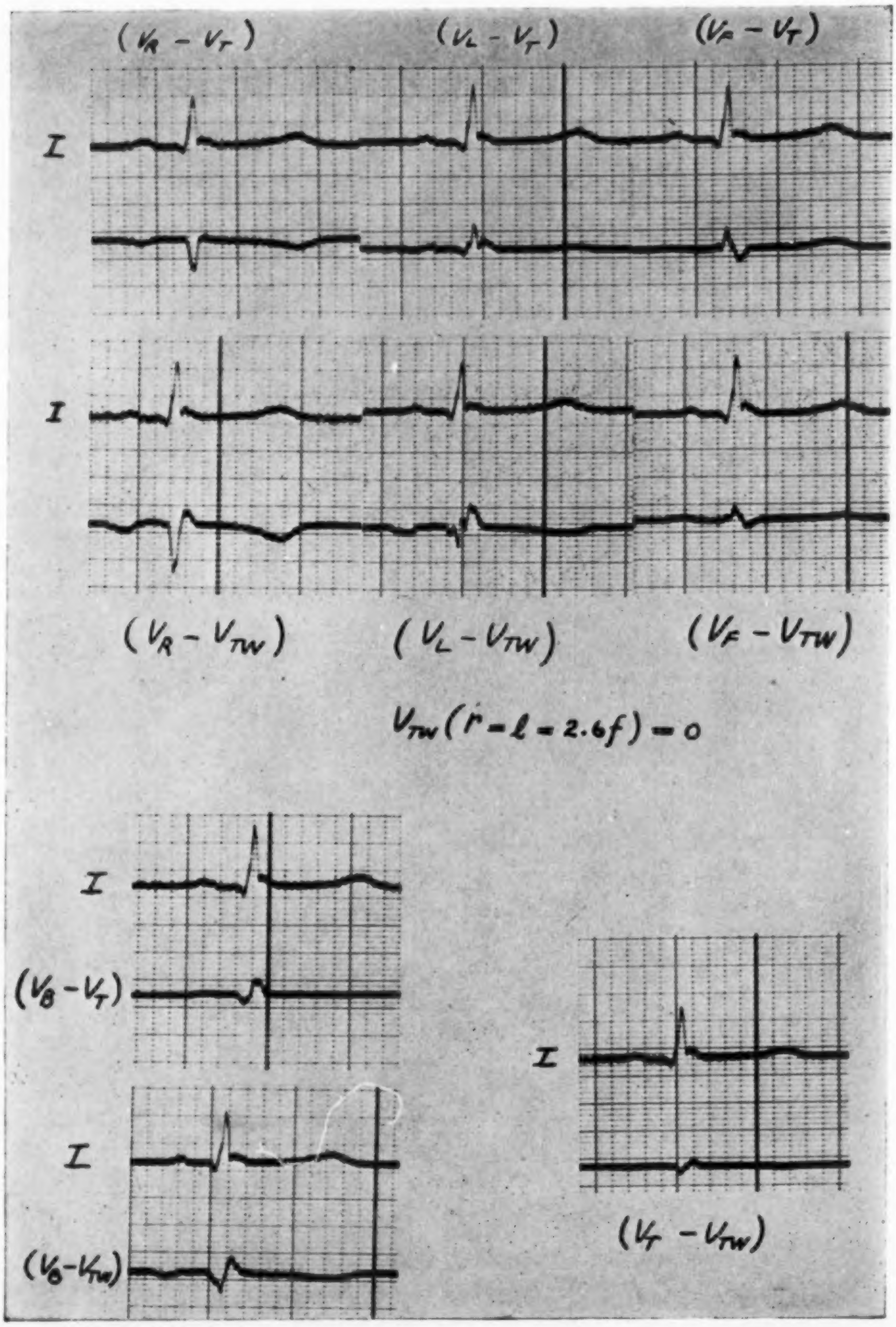


Fig. 2*B*.—True potential variations on the electrodes (R), (L), (F), and (B) with respect to $V_{TW} = 0$. The true potential variations of the Wilson (unweighted) terminal are shown in the lead $(V_T - V_{TW})$.

of the lead $(V_F - V_{TW}) = V_F$ shows that the true variations on the (F) electrode are of RS form. Consequently, if the error on $V_T \neq 0$ is essentially due to the $E_y \sim V_F$ component of the heart's field, this error must be diphasic and of QR form when V_F is of RS form. Inspection of the lead $(V_T - V_{TW})$ in fact shows a QR form.

The electrocardiograms which were recorded from subject three were chosen primarily for three reasons. The true potential variations on the (F) electrode are of opposite phase, qR, from those variations shown at the (F) electrode of subject two. The true potential variations at the (F) electrode on subject three are shown in the lead $(V_F - V_{T\omega}) = V_F$, Fig. *3B*. The error on $V_T = 0$ in subject three is of rS form and has a maximum value of 0.52 millivolt which is the largest value obtained in the subjects studied. Under the circumstances, it seemed desirable to compare this error with that of the terminal TW(r = l = 2.6f) of potential V_{TW}. This error is shown in the lead $(V_{TW} - V_{T\omega}) = V_{TW}$, Fig. *3B*. We observe that the error on the unweighted terminal of potential V_T is 3.4 times the error on the weighted terminal of potential V_{TW}. The error encountered on V_T swings from 0 to −0.52 millivolt in young normal adult subjects. The error on V_{TW} swings from 0 to +0.15 in a similar group of subjects. The average value of the former is −0.26 millivolt and that of the latter is +0.075 millivolt. The superior features of the weighted terminal TW(r = l = 2.6f) are thus obvious. Inasmuch as the true potential variations at electrodes (R), (L), (F), and (B) for subject three are shown by pairing the exploring electrode with the 4-branch weighted terminal of potential $V_{T\omega} = 0$, we may observe the influence of the unweighted terminal T(r = l = f) and the influence of the weighted terminal TW(r = l = 2.6f) by a study of the associated leads which are mounted, respectively, above and below the true variations on these electrodes, Figs. *3A* and *3B*.

REMARKS ON THE ZERO POTENTIAL OF THE HEART'S FIELD

A general description of the electrical effects produced throughout the body by the heart beat which is unlikely to receive objection on the part of serious students of the subject may be stated as follows. Cardiac excitation creates a complex of electric dipoles within the heart's substance. The complex, whenever it exists, produces an electric field throughout a nonhomogeneous linear (resistive) medium of volumetric form (body trunk). The field extends to the irregular (skin) surface of the conducting medium. How is it possible to define a zero of potential of a field generated in this manner and distributed throughout a medium of this kind and have the zero of potential thus defined available as a reference point for study of the field potentials produced by the heart beat? The midpoint potential of a single dipole is zero if the medium is homogeneous and is not zero if the medium is nonhomogeneous. Experiments which include generating a field due to a single electric dipole in a volume conductor do not permit a zero of potential at the midpoint of a resistance which shunts the electrodes. The potential at any point of the shunt resistance is sensitive to a contact resistance at the junction of the electrode tips with the homogeneous medium, and this resistance differs generally for each electrode. If the medium

is nonhomogeneous (biologic tissues) the electrode contact resistances differ in a more striking manner and change whenever the electrode position is changed.[2] It is undesirable to define or even attempt to define the zero potential of the heart's field as equivalent to some point on a shunt resistance of a dipole generating circuits. Nevertheless, Helm[5] refers to such a potential

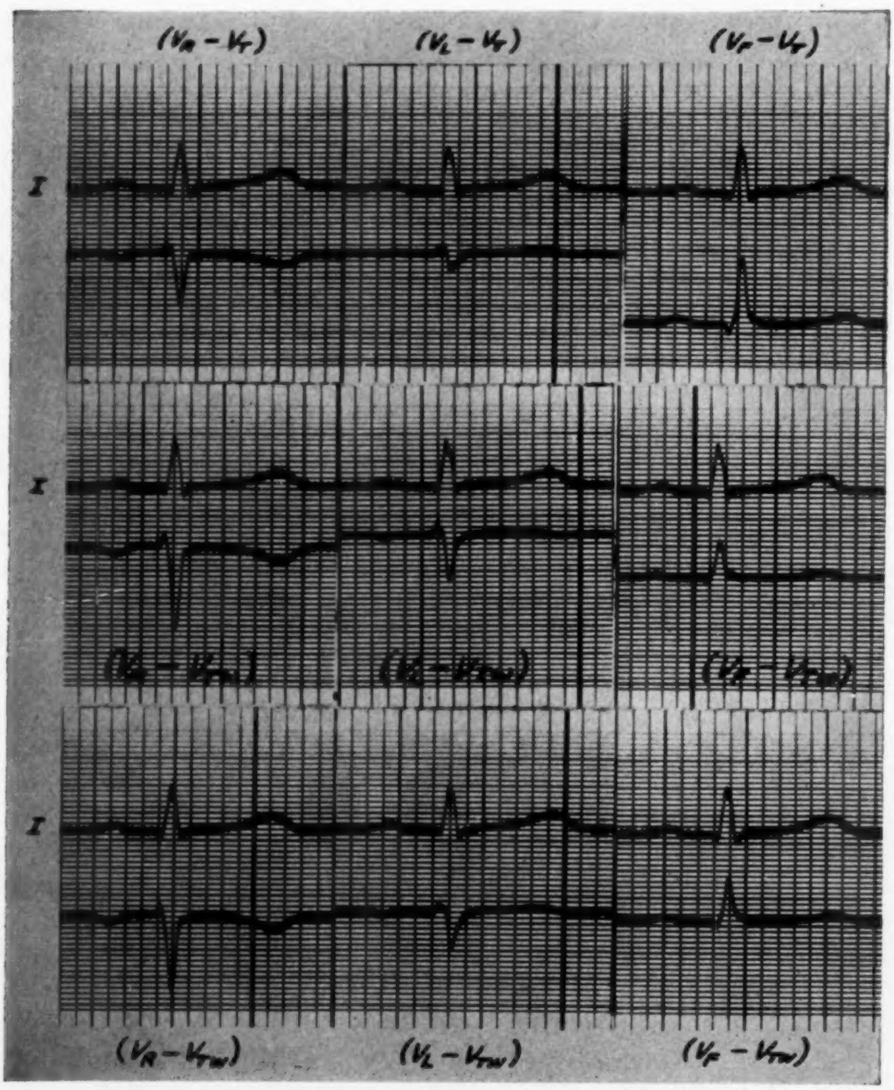


Fig. 3A.—The true potential variations on the extremity electrodes with respect to the terminal of potential $V_{T\omega} = 0$, middle row. Similar leads showing the influence of the terminal of potential $V_T \neq 0$, top row. Similar leads showing the influences of the terminal of potential $V_{TW} \neq 0$, bottom row.

as a "true zero reference potential" in a discussion of Frank's torso models. There is, however, no objection to this reference point as Frank and Kay used it,[6] but Helm fails to point out that Frank took this reference potential directly from the dipole field in a symmetrical tank where the point chosen was in the

zero-potential plane of the tank's field. The point on the shunt resistance was adjusted to that of the zero-potential plane. Moreover, the point on the shunt resistance is extremely critical and somewhat unstable and requires a recheck after each measurement together with repeated readjustments. Since no zero-

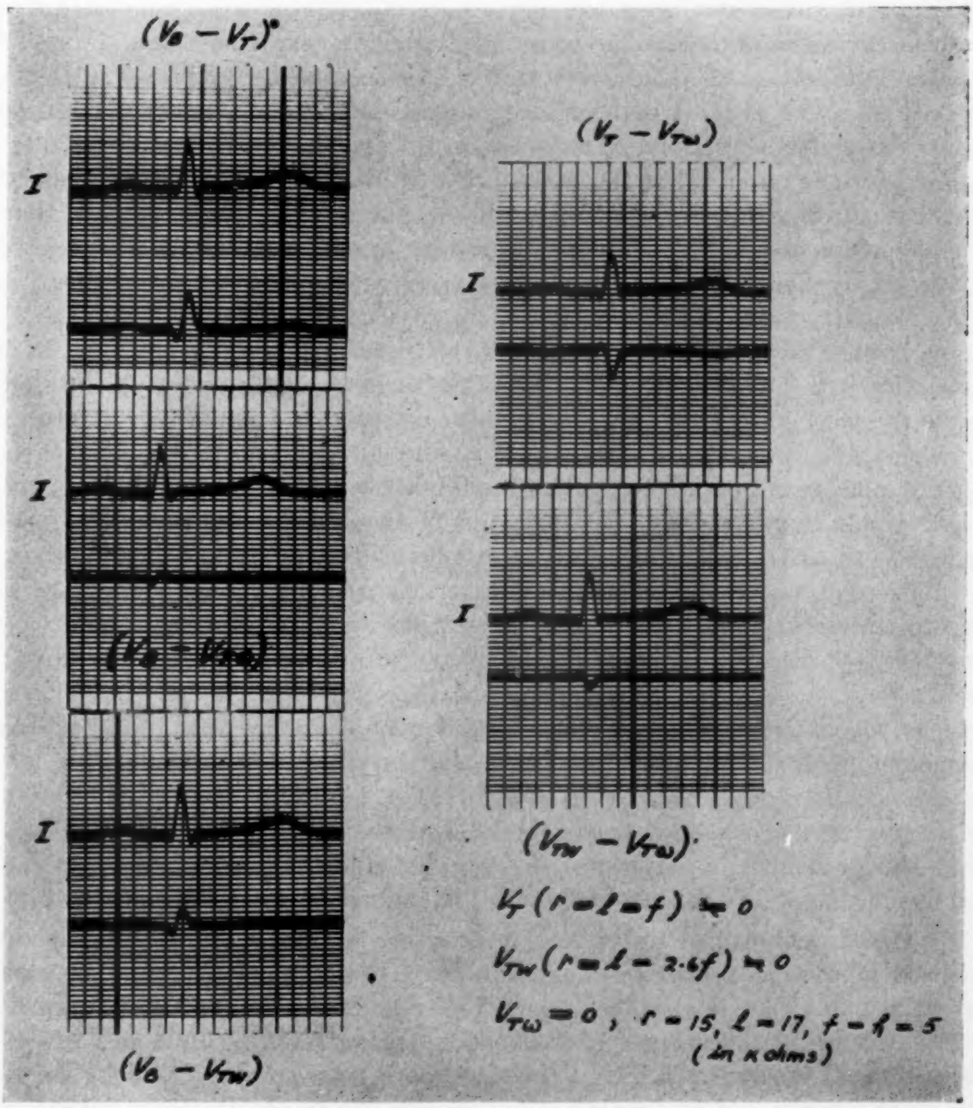


Fig. 3*B*.—Showing the true and influenced variations on the electrode (B) for the same subject as in Fig. 3*A*. The true potential variations on the terminal of potential V_T and on the terminal of potential V_{TW} are shown in the leads ($V_T - V_{T\omega}$) and ($V_{TW} - V_{T\omega}$), respectively.

potential plane is produced by the heart's complex of dipoles or even by the heart's resultant dipole, a zero reference which in any way depends upon a zero-plane must be rejected for any consideration which deals directly with the living subject.

From the time of his earlier contributions, Wilson has repeatedly emphasized the importance of choosing a remote point in the conducting medium as a reference potential with which to study bio-electrical fields.[7-9] His central terminal is at the average value of the potential at three remote points, the values of which at any instant differ in sign. In searching for a solution to the problem of a zero of potential, the importance of a remote point cannot be overemphasized. The potential due to a complex of dipoles reduces to the potential of a single dipole at distances remote from the complex.[10] The potential of a single dipole decreases with the inverse square of the distance from the dipole to the point of observation. The question arises as to how great a distance is required for the potential at the remote point to be constant or to be unaffected by the electromotive forces which vary the potential of the central terminal. The difficulties posed by this question can be avoided by making use of a theorem developed by Gauss which states that the average value of the potential due to a pole (source or sink) over the surface of a sphere which contains the pole is equal to the product of the pole and the reciprocal of the radius of the sphere.[11] This value is the same as would occur if the pole were at the center of the sphere and is therefore zero if two poles of equal magnitude and unlike sign are located anywhere within the sphere; and in fact is zero for any complex of poles wherein the net pole strength is zero. The medium, however, must be homogeneous or effectively homogeneous. If the radius of the sphere is made large in comparison with the average radius of the nonhomogeneous portion of the content, the nonzero potential on the averaging spherical surface can be made to approach zero to the desired limit. These considerations led to experiments which have established a satisfactory workable definition of the zero of potential for the heart's field.[2-4] We may therefore define the zero of potential of the heart's field as the average value of the potential over the surface of a large (6-foot diameter) integrating spherical electrode which contains the subject and a homogeneous conducting medium (tap water). The high skin resistance permits a small current flow exterior to the body, and the potential distribution in the body during immersion does not differ appreciably, except in a proportional way, from that which obtains before or after immersion.

Let the potential of the spherical electrode be denoted by V_O. The three subjects whose electrocardiograms have been presented were found to satisfy the relations $(V_T - V_O) = 0$, $(V_{TW} - V_O) = 0$, and $(V_{T\omega} - V_O) = 0$ in that order. These measurements or balance operations were conducted at seven times normal sensitivity which somewhat more than compensated for the proportional decrease of body surface potentials which results from introducing the immersion fluid and expanding the field limits. If the potential of the central terminal is not zero it must vary. If the potential V_O is not zero, it must likewise vary with the heart's field axis and the medium is effectively nonhomogeneous. Geometrical considerations exclude equal variations of the central terminal and the sphere. Therefore, satisfying these equations is equivalent to showing that V_T in the first subject, V_{TW} in the second subject, and $V_{T\omega}$ in the third subject are equal to V_O and are zero. We are in full agreement with Helm,[5] therefore, when he presents an essentially similar theoretical

argument for showing that $V_T = 0$ if the relation $(V_{P1} - V_T) = K(V_{P2} - V_T)$ can be satisfied for values of $K \neq 1$ and wherein P_1 and P_2 are a pair of electrodes which include the heart between them. Experiments which attempt to balance the potentials of two terminals, one the 3-branch central terminal of potential V_{T3} and the other a 2-branch terminal of potential V_{T2} connected to the electrodes P_1 and P_2, are of essentially the same kind and require one detector. Some four years ago we had little success with experiments of the latter kind. Varying all resistances in both terminals is permitted, and a failure to satisfy $V_{T3} = V_{T2}$ proves nothing; in particular it is not shown that $V_{T3} \neq 0$ or that $V_{T2} \neq 0$.

CONCERNING TORSO MODELS

Our studies upon the living human subject[3] are in considerable disagreement with studies performed upon homogeneous torso models.[12-14] Frank has shown that in the homogeneous torso model the R′, L′, F′ plane does not contain zero and consequently the Wilson central terminal for the torso model must have a nonzero limit. In the torso model the "heart region" is anterior to the R′, L′, F′ plane. Frank further suggests that the torso model coefficients be tentatively adapted for clinical use in the belief that "far less error" would be incurred than by using the currently accepted standard system of leads. It should be pointed out, however, that the "heart region" of the homogeneous torso model is chosen quite arbitrarily, and this arbitrary choice reduces these experiments to an emphasis of the importance of body surface contour. It is possible, nevertheless, to approach the contour problem in an entirely different manner. The Wilson-Bayley Equation (19) for the potential at any point upon the surface of a sphere due to a contained dipole of arbitrary position has three terms in the curled brackets.[15] Only the last two of these terms depend upon surface contour, and one is always positive when the other is negative. As a result their sum gives a surprisingly small value except when the point chosen for computing the potential is on or near a line through the axis of the dipole along the radius vector from the origin to the eccentricity. If these last two terms are neglected or omitted and only the first term retained the result is Equation (17) multiplied by 2 and is the approximate solution for the potential of an arbitrary dipole in a volume conductor of any shape. We may therefore multiply by 2 our numerical answer given by Equation (17) and compare it with the result using Equation (19). In this way we obtain a numerical demonstration of the importance, or of the unimportance, of surface contour upon the potential distribution. On the other hand, the relative orientation of the dipole with respect to the electrode system is in our opinion of greater importance upon the potential distribution, and this feature must be neglected by an arbitrary choice of the "heart region" in torso model studies. The disagreement should therefore not be too surprising. Frank's awareness of the importance of dipole orientation is fully expressed in his theoretical discussion of variable dipole eccentricity.[16] Our studies on the living human subject support these theoretical considerations to the extent that respiratory motions of the heart produce small changes in the potential of the central terminal which can be eliminated by quiet

breathing.[3] These latter studies also show that V_T, V_{TW}, and $V_{T\omega}$, unlike the torso model terminal, certainly contain zero-potential limits, and the error on V_{TW} appears to be within the tolerance of most clinical purposes.

Suggestions for a standardization of vectorcardiographic leads at this time are premature, and standardization may have the effect of increasing the already overburdened preoccupation of recording "vectorcardiograms" of various kinds. The lack of accepted standards may encourage studies aimed at solution of the lead problem. Appropriate vectorcardiographic leads should incorporate the $\vec{E}_x$, $\vec{E}_y$, and $\vec{E}_z$ components of the heart's field unaffected by the asymmetrical electrical properties of the body trunk.

SUMMARY AND CONCLUSIONS

1. The true potential variations of the extremity and back electrodes (R), (L), (F), and (B) and of the precordial electrodes are demonstrated.
2. The influence of central terminal networks of nonzero potential upon the true potential variations of extremity, back, and precordial electrodes is also demonstrated.
3. Central terminal networks of two kinds, unweighted or $T(r = l = f)$ and weighted or $TW(r = l = 2.6f)$, are discussed and examples of their maximum errors in normal young adult subjects are demonstrated. The error on the former is 3.4 times the error on the latter.
4. The problem posed by a workable definition of the zero of potential of the heart's field is briefly discussed, and a solution offered elsewhere is emphasized.
5. Studies in the living human subject are in considerable disagreement with those conducted upon homogeneous torso models. The arbitrary "heart region" in the latter reduces these studies to an emphasis on the effect of body contour upon the potential distribution. The contour effect is discussed briefly from a purely numerical approach, and the greater importance of dipole orientation is emphasized.
6. Standardization of vectorcardiographic leads at this time is rejected as premature. Preoccupation with recording and describing vectorcardiograms of various kinds is also premature, and it is hoped that more of this energy will be directed toward a solution of the lead problem.

SUMMARIOS E CONCLUSIONES IN INTERLINGUA

1. Le ver variationes de potential in le electrodos (R), (L), (F), e (B) del extremitates e del dorso e in le electrodos precordial es demonstrate.
2. Le influentia del retes del termino central a potentiales non-zero super le ver variationes de potential in le electrodos del extremitates, del dorso, e del precordio es etiam demonstrate.
3. Es discutite retes de termino central de duo typos: le typo non-ponderate o $T(r = 1 = f)$ e le typo ponderate o $TW(r = 1 = 2, 6f)$. Exemplos de lor errores maximal in juvene masculos es demonstrate. Le error in le typo non-ponderate es 3, 4 vices le error in le typo ponderate.

4. Es presentate un breve discussion del problema de un usabile definition del zero de potential in le campo del corde. Es sublineate le valor de un solution que ha essite publicate in un altere loco.

5. Studios in vive subjectos human es in forte disaccordo con studios conducite per medio de homogenee modellos del torso. Le arbitrari "region cardiac" in tal modellos fortia le investigator a concentrar su attention super le effecto que es exercite per le contorno del corpore super le distribution de potentiales. Le effecto del contorno es discutite brevemente ab un puncto de vista purmente numeric. Es sublineate in contrasto le plus alte importantia del orientation del dipolo.

6. Le standardisation de derivationes vectocardiographic a iste tempore es considerate como prematur. Etiam le preoccupation con le registration e description de varie vectocardiogrammas es prematur. Il es a sperar que le energia absorbite per iste activitates va plus tosto esser dedicate al solution del problema del derivationes.

REFERENCES

1. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent Potential Variations of a Single Electrode, Am. Heart J. **9**:447, 1934.
2. Bayley, R. H., and Kinard, C. L.: The Zero of Potential of the Electric Field Produced by the Heart Beat. The Problem With Reference to the Living Subject, Circulation Res. **2**:104, 1954.
3. Bayley, R. H., and Schmidt, A. E.: The Problem of Adjusting the Wilson Central Terminal to a Zero of Potential in the Living Human Subject, Circulation Res. **3**:94, 1955.
4. Bayley, R. H., Reynolds, E. W., Jr., Kinard, C. L., and Head, J. F.: The Zero of Potential of the Electric Field Produced by the Heart Beat. The Problems With Reference to Homogeneous Volume Conductors, Circulation Res. **2**:4, 1954.
5. Helm, R. A.: Theory of Vectorcardiography: A Review of Fundamental Concepts, Am. Heart J. **49**:135, 1955.
6. Frank, E., and Kay, C. F.: A Reference Potential for Unipolar Electrocardiographic Measurements on Models, Am. Heart J. **46**:195, 1953.
7. Wilson, F. N.: The Distribution of the Potential Differences Produced by the Heart Beat Within the Body and at Its Surface, Am. Heart J. **5**:599, 1930.
8. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., and Barker, P. S.: On Einthoven's Triangle, the Theory of Unipolar Electrocardiographic Leads, and the Interpretation of the Precordial Electrocardiogram, Am. Heart J. **32**:277, 1946.
9. Wilson, F. N.: On the Choice of a Reference Point for the Study of the Electrical Field of a Tissue Immersed in a Volume Conductor. Libro Homenaje al Profesor I. Chavez, Edit. Univer. Nac. Auton., Mexico, 1945.
10. Straton, J. A.: Electromagnetic Theory, New York, 1941, McGraw-Hill Book Company, page 183.
11. Kellogg, O. D.: Foundations of Potential Theory, New York, 1943, Fredric Ungar.
12. Frank, E., and Kay, C. F.: Frontal Plane Studies of Homogeneous Torso Models, Circulation **9**:724, 1954.
13. Frank, E.: The Image Surface of a Homogeneous Torso, Am. Heart J. **47**:757, 1954.
14. Frank, E.: General Theory of Heart-vector Projection, Circulation Res. **2**:258, 1954.
15. Wilson, F. N., and Bayley, R. H.: The Electric Field of an Eccentric Dipole in a Homogeneous Spherical Conducting Medium, Circulation **1**:85, 1950.
16. Frank, E.: Theoretic Analysis of the Influence of Heart Dipole Eccentricity on Limb Leads, Wilson Central-Terminal Voltage and the Frontal Plane Vectorcardiogram, Circulation Res. **1**:380, 1953.

STUDIES OF C-REACTIVE PROTEIN IN PATIENTS WITH RHEUMATIC HEART DISEASE

I. Lack of Correlation Between C-Reactive Protein and Aschoff Bodies in Left Auricular Appendage Biopsies

Samuel K. Elster, M.D.,* and Harrison F. Wood, M.D.

New York, N. Y.

THE finding of Aschoff bodies in a fairly large proportion of left auricular appendages amputated at the time of mitral commissurotomy in patients with rheumatic mitral stenosis has renewed interest in the pathologic criteria for the diagnosis of acute rheumatic carditis. Histopathologic lesions thought to be characteristic of acute carditis have been detected in such biopsies in many instances in which there was no clinical suspicion of acute rheumatic carditis.[1-5] The significance of the pathologic findings has been disputed. Some[1] believe that they represent continued "smoldering" of the rheumatic process long after the clinically active acute rheumatic fever has subsided and, as such, may contribute to the course and outcome of chronic rheumatic heart disease. Others[5] believe that they are incidental histopathologic findings without significance.

A study[6] of patients with mitral stenosis following mitral commissurotomy has failed to demonstrate differences in survival, reactivation of acute rheumatic fever, or occurrence of the postcommissurotomy syndrome related to the presence or absence of Aschoff bodies in the auricular biopsies. Sensitive clinical and laboratory tests designed to detect acute rheumatic fever have failed to indicate any correlation with the histopathologic findings in the left auricular appendage.[2,7,8] Although McNeely and associates[7] found no significant association between biopsy findings and the antistreptolysin-O titer, Biörck found two instances in which the antistreptolysin-O titer was elevated in which Aschoff bodies were present in the auricle, although four other patients had positive biopsies and normal antistreptolysin-O titers.

The C-reactive protein, an abnormal protein absent from the sera of normal patients, is present in the blood in a variety of diseases.[9,10] It is a very sensitive, although nonspecific, indicator of acute rheumatic fever.[11,12] The present study proposes to correlate the C-reactive protein as well as other clinical and laboratory tests for acute rheumatic fever with the histopathologic findings in auricular appendages resected at operation on twenty patients with rheumatic mitral stenosis.

From the Departments of Medicine, Pathology and Microbiology, The Mount Sinai Hospital, and the Hospital of the Rockefeller Institute for Medical Research, New York, N. Y.

Received for publication March 15, 1955.

*Elsa and William Menke Fellow in Medicine.

MATERIALS AND METHODS

The twenty patients comprising this study were from the Medical and Surgical Services of The Mount Sinai Hospital. They ranged in age from 28 to 50 years. Fifteen were women and five were men; eighteen were white and two were Negro. In each patient, the indication for mitral commissurotomy was myocardial insufficiency of varying degree. In addition, four patients had prominent hemoptysis, and two had histories of systemic embolism. All patients had mitral stenosis; three had associated mitral insufficiency, three probable mild aortic insufficiency, and one aortic stenosis. All patients were carefully selected so that none was operated upon who had overt acute rheumatic fever of even suspicion of moderate rheumatic activity.

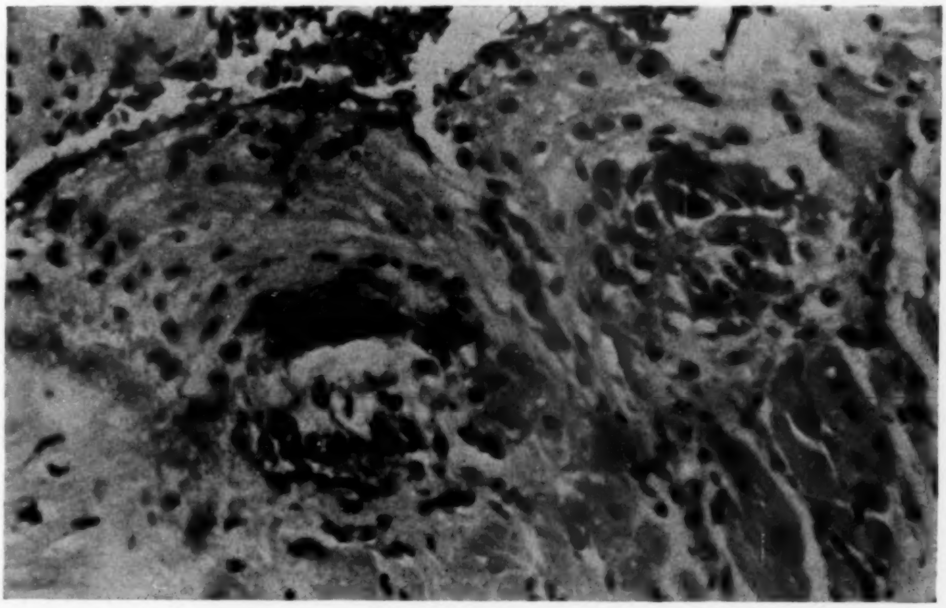


Fig. 1.—Aschoff bodies in left auricular subendocardium, demonstrating typical cellular morphology.

In addition to the clinical examination, preoperative study included appropriate roentgenographic, electrocardiographic, and cardiac catheterization determinations. Urine analysis, complete blood count, erythrocyte sedimentation rate (Westergren method), antistreptolysin-O determinations,[13] and tests for C-reactive protein were made in each instance.

Serum was analyzed for the presence of C-reactive protein according to the method of Anderson and McCarty.[11] C-reactive protein antiserum (1.5 cm.) and an equal amount of the patient's serum were drawn into a capillary tube (0.7 to 1.0 mm. outside diameter). The tube was incubated at 37.5°C. for two hours and refrigerated at 4°C. overnight. Where no visible precipitate was present, the test was considered negative. Each millimeter of precipitate was considered 1-plus with the maximum precipitation equal to 8-plus.

At operation, the left auricular appendage was amputated and a finger-fracture mitral commissurotomy was performed. The auricular appendage was fixed in neutral formalin solution. Multiple sections were made; these were stained with hematoxylin and eosin and were studied microscopically for the presence of Aschoff bodies, inflammatory reaction, fibrosis, and muscular changes. The Aschoff body was defined[14,15] as ". . . disorganization in the fibrous tissue in which it occurs, the collagenous fibers showing swelling, eosinophilia, granular degeneration or necrosis. The degenerative change is accompanied by a rather special sort of inflammatory infiltrate in which large,

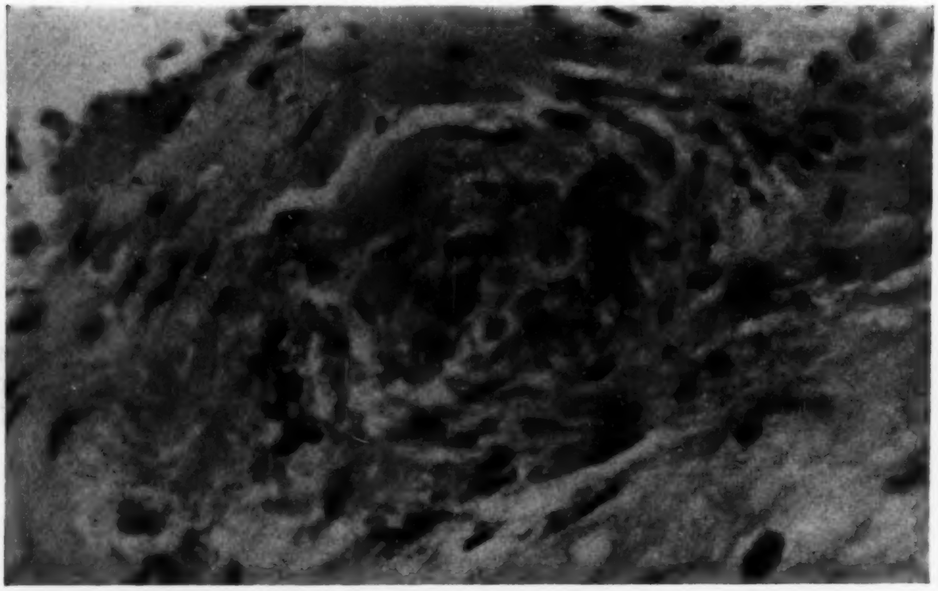


Fig. 2.—Aschoff body in left auricular subendocardium, demonstrating swelling and fragmentation of connective tissue.

irregular cells with ragged edges, basophilic cytoplasm and one or more vesicular nuclei with 'owl-eyed' nucleoli are present. In addition, various other less characteristic cells may be present; for instance, lymphocytes, plasma cells and histiocytes."

RESULTS

A. *Histopathologic Data.*—Aschoff bodies were detected in seven of the twenty specimens (Figs. 1, 2). There was no correlation between the presence of Aschoff bodies and the findings of nonspecific inflammatory reaction or muscular hypertrophy (Table I). In many instances, the inflammatory cells were lymphocytes, located primarily in the pericardium. There were six instances of auricular thrombi, in none of which was there evidence of any Aschoff body, although subjacent nonspecific inflammatory infiltrates occurred in five cases.

The left auricular biopsy specimen obtained from patient, J. D., did not contain Aschoff bodies. The patient died several days postoperatively. At necropsy, no gross or microscopic evidence of acute rheumatic myocarditis was obtained.

TABLE I. CORRELATION OF ASCHOFF BODIES WITH INFLAMMATORY REACTION, MUSCLE HYPERTROPHY, AND THROMBI IN AURICULAR APPENDAGE BIOPSIES

	NUMBER	INFLAMMATORY REACTION	MUSCLE HYPERTROPHY	THROMBI
Aschoff bodies	7	2	7	0
No Aschoff bodies	13	7	8	6

B. *Clinical Data.*—There were no discernible clinical differences between the seven patients who had auricular biopsies positive for Aschoff bodies and the remaining thirteen patients who did not (Table II). Age and sex distributions were approximately the same, and there was no difference in the length of time since the most recent attack of acute rheumatic fever. Joint pains, skin eruptions, subcutaneous nodules, and changing heart murmurs were absent. All patients had normal preoperative temperatures, except for transitory rises in three. In one (I.M.), there were two days of temperature of 100.4° F. at the time of admission to the hospital. Patient J.S. had fever associated with a urinary tract infection and on another occasion with a respiratory infection, both of which responded to the administration of antibiotics. Patient J.D. had two days of temperature elevation to 100.8° F. associated with an increase of congestive heart failure. In these three cases, the temperature was normal for at least two weeks preoperatively.

C. *Laboratory Data.*—The urine of all patients was normal. Anemia was uniformly absent. Unexplained leukocytosis was encountered in two cases and a rapid erythrocyte sedimentation rate in one instance in the group of seven patients in which the auricular biopsy contained Aschoff bodies. Of the remaining thirteen patients whose auricular appendages did not contain Aschoff bodies, one patient had leukocytosis and two had rapid erythrocyte sedimentation rates. In none of the twenty patients was there clinical or laboratory evidence of a streptococcal infection. However, of the seven patients with positive biopsies, only three had titers of antistreptolysin-O within the range of normal. Three patients had slightly elevated levels, and one had a markedly elevated titer of antistreptolysin-O. Ten of the thirteen patients with negative auricular biopsies had titers of antistreptolysin-O within the normal range whereas only two had slight elevations of titer, and one had marked elevation of titer. The numbers of patients in these groups are too few to warrant any conclusions.

Studies for C-reactive protein were carried out preoperatively in serial bleedings in most instances, although in some patients only single blood specimens were available (Table II). Five of the seven patients whose auricular

biopsies contained Aschoff bodies did not have C-reactive protein in blood specimens taken preoperatively. Two patients, E.K. and J.S., had C-reactive protein in their blood intermittently in the preoperative period. In the former patient, a 1-plus level of C-reactive protein was detected in the blood at the time of hospital admission without any apparent cause. The abnormal protein was not present in a subsequent blood sample, but returned (5-plus) following a bout of pulmonary edema. Two subsequent bleedings contained no C-reactive protein. The positive values for C-reactive protein obtained in patient J.S. were associated with congestive heart failure (1-plus), following cardiac catheterization (6-plus) and after a bout of pulmonary edema (±). Three other blood specimens contained no C-reactive protein.

TABLE II. CLINICAL AND LABORATORY DATA OF TWENTY PATIENTS WITH RHEUMATIC MITRAL STENOSIS SUBJECTED TO MITRAL COMMISSUROTOMY

PATIENT	AGE	SEX	YEARS SINCE LAST ATTACK OF ACUTE RHEUMATIC FEVER	WHITE BLOOD COUNT (CELLS/ CU.MM.)	ERYTHROCYTE SEDIMENTATION RATE (WESTERGREN) (MM./HR.)	ANTI-STREP-TOLYSIN O TITER (UNITS)	SERIAL PREOPERATIVE C-REACTIVE PROTEIN DETERMINATIONS	ASCHOFF BODIES IN LEFT AURICULAR BIOPSY
E.C.	39	M	33	14,000	7	317	0,0,0,0,0,0	+
E.K.	29	F	?	8,800	28	1,000	1+,0,5+,0,0	+
I.M.	34	F	?	9,300	15	317	0,0	+
S.P.	31	M	?	9,300	3	50	0	+
R.R.	42	F	21	7,800	22	317	0	+
J.S.	33	F	21	11,500	21	200	1+,0,0,6+,±,0	+
C.T.	46	F	31	9,000	8	50	0,0	+
A.B.	50	F	23	5,000	16	1,000	0	0
W.B.	28	M	10	7,550	8	317	0,0	0
G.B.	32	F	19	7,700	29	159	0	0
F.C.	30	M	?	7,900	2	83	0	0
E.C.	38	F	32	7,300	8	159	0	0
J.D.	47	F	?	7,300	16	200	0	0
F.G.	38	F	24	11,650	21	317	1+,6+	0
R.G.	41	F	?	7,000	23	100	0,0	0
E.H.	37	F	?	9,200	6	159	1+,±,±,0,±	0
Y.K.	42	F	31	6,950	5	50	0	0
R.L.	33	F	?	9,000	43	50	1+,2+,2+,1+,0,± 0,0,0,0,0,0,0,0,0	0
E.M.	32	F	22	6,350	7	125	0	0
H.C.	46	M	?	8,800	22	125	1+	0

C-reactive protein was not present in preoperative blood samples taken from nine of the thirteen patients whose auricular appendages did not contain Aschoff bodies. No obvious cause was noted for the 1-plus level of C-reactive protein in patient F.G., although a 6-plus level appeared following cardiac catheterization. The small amount of C-reactive protein detected in the blood of patient E.H. was associated with severe congestive heart failure. Following medical therapy, the patient lost 15 pounds of edema fluid. Trace amounts of C-reactive protein persisted in her blood. The initial blood samples of R.L. also contained small amounts of C-reactive protein. Following diuretic treatment and subsequent improvement of the state of congestive heart failure, the C-reactive protein disappeared from the blood. The presence of C-reactive protein in the blood of patient H.C. is unexplained.

DISCUSSION

The demonstration of Aschoff bodies in seven of twenty auricular appendages of the patients in this series is confirmation of similar results published by other authors.[1-5,7,14] Kuschner and Levieff[16] and McKeown[17] have studied post-mortem material in order to determine whether the presence of microscopic evidence of rheumatic carditis in the auricular appendage reflects similar findings elsewhere in the heart. In the former study, nine of forty rheumatic hearts examined at necropsy contained subendocardial Aschoff bodies in the left auricular appendage. All of these nine cases had active lesions in other regions in the heart. Six of the forty hearts had evidences of activity in other sites, although the left auricular appendages were inactive. McKeown confirmed this in seventeen cases having Aschoff nodules in the left auricular appendage as well as in other parts of the heart. The presence of Aschoff bodies in the left auricular appendage would seem to indicate that lesions are very likely to be present elsewhere in the heart, whereas the absence of these lesions in the appendage does not preclude the possibility of activity at other sites in the heart.

Other investigators have failed to provide a positive correlation of the histologic findings of rheumatic activity in the auricular appendages with clinical or laboratory evidence of active rheumatic fever in the patient. McNeely and associates[7] found no relation between positive biopsies to fever, electrocardiographic abnormalities, elevated erythrocyte sedimentation rate, leukocytosis, or elevated antistreptolysin-O titer. They did find a diminished incidence of positive biopsies in older patients, in those with auricular fibrillation and in those with auricular thrombi. Others, however, have noted increased erythrocyte sedimentation rate[3] and increased antistreptolysin-O titer[2] in some instances in which the auricular biopsies contained Aschoff bodies, although no well-defined correlation was obtained.

None of the patients in our series fulfilled the criteria[8,18] for the diagnosis of acute rheumatic fever. No relationship was evident between the positive auricular biopsies and leukocytosis or increased erythrocyte sedimentation rate. Although the incidence of elevated antistreptolysin-O titers was greater in the group which contained Aschoff bodies than in their absence, the number of cases is too small to warrant conclusions.

The C-reactive protein appears as an acute phase response in a variety of abnormal conditions such as trauma, infections, necrosis, neoplasia, and granuloma formation.[9,10] It has been characterized as a beta globulin by free electrophoresis and is apparently combined with lipid in vivo.[19] In acute rheumatic fever,[11,12] it has been found to be an excellent indicator of the disease activity and, hence, has been used as a guide for treatment and management of patients. Despite its lack of specificity, it has often proved more useful than other nonspecific indicators, such as the erythrocyte sedimentation rate or white blood count. If the positive biopsies in the patients reported here were indicative of acute rheumatism, one would have expected that the blood of these patients would have contained C-reactive protein preoperatively. Conversely, persistent absence of C-reactive protein from the patient's blood would have sug-

gested that if activity were present, it was not of sufficient severity to lead to the production of this abnormal protein.

Of the seven patients who had positive biopsies, the blood of only one contained C-reactive protein without known cause. Of the thirteen patients who did not have Aschoff bodies in the auricular appendage, two patients had C-reactive protein in their blood preoperatively without known cause. In the remaining patients with or without Aschoff bodies in the appendage in whose blood C-reactive protein was detected, the presence of the abnormal protein was ascribed to trauma or congestive heart failure.[20] Thus, the appearance of C-reactive protein in the patient's blood preoperatively did not correlate with the presence of Aschoff bodies in the left auricular appendage.

The finding of Aschoff bodies in left auricular appendages correlates well with the presence of Aschoff bodies elsewhere in the heart. It is believed by most observers that the presence of Aschoff bodies in the myocardium at necropsy indicates probable persistent anatomic evidence of rheumatic activity. The C-reactive protein has been found to be always present in instances of acute rheumatic fever, except in cases of pure chorea. The failure of the C-reactive protein to correlate with the presence of Aschoff bodies in the left auricular appendage would indicate that the pathologic process is not sufficiently active to lead to the production of the C-reactive protein. In such cases with no C-reactive protein detected in the blood, the degree of rheumatic activity may have little or no clinical significance. This is confirmed by the lack of difference of the postoperative course, reactivation of overt acute rheumatic fever and incidence of the postcommissurotomy syndrome irrespective of the presence of Aschoff bodies in the auricular appendage.[6]

SUMMARY AND CONCLUSIONS

Left auricular appendage biopsies were obtained at the time of mitral commissurotomy from twenty patients with rheumatic mitral stenosis. Seven biopsies contained Aschoff bodies in the auricular subendocardium.

There were no significant differences between the group that contained Aschoff bodies and those that did not, in regard to age, sex, duration of heart disease, fever, electrocardiographic abnormalities, white blood cell count, or erythrocyte sedimentation rate. The antistreptolysin-O titers were elevated in four of the seven cases whose biopsies were positive for Aschoff bodies, as compared to three elevated titers of thirteen patients whose auricular biopsies were negative.

There was no correlation evident between the presence of C-reactive protein in preoperative bleedings and the presence of positive auricular biopsies. Only two of seven patients with positive biopsies had C-reactive protein in their sera preoperatively, whereas C-reactive protein was present in four of the remaining thirteen patients with negative auricular biopsies.

The failure of correlation of the C-reactive protein with the presence of Aschoff bodies in the auricular subendocardium may indicate that the pathologic process is not sufficiently active to lead to the production of this abnormal

protein. In such cases, with no C-reactive protein detected in the blood, the degree of rheumatic activity may have little or no clinical significance.

The authors are deeply grateful to Drs. S. Otani and A. Bernheim, who performed the pathologic studies, Drs. M. Ravitch, A. Himmelstein, L. Blum and R. Nabatoff, who operated upon these patients, and Mrs. Fela Polishuk and Evelyn Eason, who performed the antistreptolysin-O determinations.

SUMMARIO IN INTERLINGUA

Esseva studiate 20 patientes con rheumatic stenosis mitral ante le execution de commissurotomia mitral. In 7 del 20 casos, specimens bioptic obtenite ab le annexo sinistro-auricular durante le operation revelava le presentia de corpores de Aschoff. Le presentia o absentia del corpores de Aschoff non pareva corresponder a ulle discernibile differentia de etate, sexo, duration del morbo cardiac, febre, anormalitates electrocardiographic, conto leucocytic, o sedimentation del erythrocytos. Titros elevate de antistreptolysina-O esseva plus commun in le gruppo con corpores de Aschoff, sed il non esseva possibile establir un correlation inter le presentia de proteina C-reactive in le sanguination preoperative e le presentia de positive biopsias auricular. Nostre studio indica que le processo pathologic in le corde non es satis active pro causar le production de proteina C-reactive e que le activitate rheumatic ha possibilemente pauc o nulle signification clinic.

REFERENCES

1. Kuschner, M., Ferrer, M. I., Harvey, R. M., and Wylie, R. H.: Rheumatic Carditis in Surgically Removed Auricular Appendages, AM. HEART J. **43**:286, 1952.
2. Biörck, G., Winblad, S., and Wulff, H. B.: Studies in Mitral Stenosis. II. Observations on Incidence of Active Rheumatic Carditis in Left Auricular Appendages Resected at Operation for Mitral Stenosis, AM. HEART J. **44**:325, 1952.
3. Sabiston, D. C., and Follis, R. H.: Lesions in Auricular Appendages Removed at Operations for Mitral Stenosis of Presumed Rheumatic Origin, Bull. Johns Hopkins Hosp. **91**:178, 1952.
4. Pinniger, J. L.: The Left Auricular Appendage in Mitral Stenosis, St. Thomas's Rep. **7**:54, 1951.
5. Enticknap, J. B.: Biopsy of the Left Auricle in Mitral Stenosis, Brit. Heart J. **15**:37, 1953.
6. Elster, S. K., Wood, H. F., and Seely, R. D.: Clinical and Laboratory Manifestations of the Post-commissurotomy Syndrome, Am. J. Med. **17**:826, 1954.
7. McNeely, W. F., Ellis, L. B., and Harken, D. E.: Rheumatic "Activity" as Judged by the Presence of Aschoff Bodies in Auricular Appendages of Patients With Mitral Stenosis. II. Clinical Aspects, Circulation **8**:337, 1953.
8. Jones, T. D.: The Diagnosis of Rheumatic Fever, J.A.M.A. **126**:481, 1944.
9. Hedlund, P.: The Appearance of Acute Phase Protein in Various Diseases, Acta med. scandinav. Suppl. **196**:579, 1947.
10. Good, R. A.: Acute-phase Reactions in Rheumatic Fever. Rheumatic Fever A Symposium, U. of Minn. Press, 1952.
11. Anderson, H. C., and McCarty, M.: Determination of C-reactive Protein in the Blood as a Measure of the Activity of the Disease Process in Acute Rheumatic Fever, Am. J. Med. **8**:445, 1950.
12. Stollerman, G. H., Glick, S., Patel, D. J., Hirschfeld, I., and Rusoff, J. H.: Determination of C-reactive Protein in Serum as a Guide to the Treatment and Management of Rheumatic Fever, Am. J. Med. **15**:645, 1953.
13. Massell, B. F., and Miller, J. M.: Technique for Producing Streptolysin and Determining Antistreptolysin-O Content of Sera, House of Good Samaritan, Boston, Mass., Dec. 1950.
14. Decker, J. P., Hawn, C. V. Z., and Robbins, S. L.: Rheumatic Activity as Judged by the Presence of Aschoff Bodies in Auricular Appendages of Patients With Mitral Stenosis. I. Anatomic Aspects, Circulation **8**:161, 1953.
15. Gross, L., and Ehrlich, J. C.: Studies on the Myocardial Aschoff Body. I. Descriptive Classification of Lesions, Am. J. Path. **10**:467, 1934.

16. Kuschner, M., and Levieff, L.: Correlation Between Active Rheumatic Lesions in the Left Auricular Appendage and Elsewhere in the Heart, Am. J. M. Sc. **226**:290, 1953.
17. McKeown, F.: The Left Auricular Appendage in Mitral Stenosis, Brit. Heart J. **15**:433, 1953.
18. Griffith, G. C., and Scheinkopf, J. A.: The Diagnosis and Differential Diagnosis of Rheumatic Fever, Acta med. scandinav. Suppl. **266**:429, 1952.
19. Wood, H. F., McCarty, M., and Slater, R. J.: The Occurrence During Acute Infections of a Protein Not Normally Present in the Blood. V. Physical-Chemical Properties of the C-reactive Protein Crystallized by a Modified Technique, J. Exper. Med. **100**:71, 1954.
20. Elster, S. K., Braunwald, E., and Wood, H. F.: Studies of C-reactive Protein in Patients With Congestive Heart Failure, (In preparation).

THE BLOOD AMMONIA IN CONGESTIVE HEART FAILURE

ALICE N. BESSMAN, M.D., AND JOHN M. EVANS, M.D.

WASHINGTON, D. C.

CONFUSION, lethargy, and coma are occasional accompaniments of congestive heart failure. The secondary occurrence of hepatic insufficiency in patients with chronic passive congestion is generally accepted.[1-3] In primary liver disease the appearance of mental disturbances and coma has been ascribed to an increased level of blood ammonia.[4-9] In view of these facts, it was thought worthwhile to investigate the level of blood ammonia in patients with congestive heart failure.

METHODS

Volunteers or comatose patients from the clinic and wards of The George Washington University Hospital were studied. The patients selected had heart disease of varying etiologies, and all showed classical signs and symptoms of right-sided congestive heart failure but were without known primary liver disease. Control subjects were patients without demonstrable heart or liver disease.

Specimens for ammonia determination were drawn without stasis within five minutes of each other from the femoral artery and either the femoral or an antecubital vein. The blood ammonia was determined by a micro diffusion-nesslerization method modified from the method of Seligson,[10] as previously described.[8] Duplicate samples and standards were run for each pair of determinations. All ammonia levels are described in terms of gamma ammonia nitrogen per cubic centimeter.

RESULTS

Table I presents the data on the arterial and venous ammonia determinations of nine control patients with various diseases but with no signs or symptoms of liver disease or of congestive heart failure. These results are within the normal range of less than 1.0 gamma/c.c. previously reported by various authors.[4,8,9,11,12] The mean arterial level is 0.77 gamma/c.c. and the mean venous level 0.83 gamma/c.c. Although the arteriovenous differences are small, there seems to be a tendency toward a negative arteriovenous difference, i.e., an evolution of ammonia from the muscles (arm or leg).

From The Department of Medicine, The George Washington University School of Medicine, Washington, D. C.

Supported in part by a grant from the Washington Heart Association, Washington, D. C.

Received for publication March 15, 1955.

TABLE I. BLOOD AMMONIA LEVELS IN CONTROL PATIENTS WITHOUT CONGESTIVE HEART FAILURE OR PRIMARY LIVER DISEASE

PATIENT	AGE	DIAGNOSIS	MENTAL STATE	BLOOD AMMONIA		A-V DIFFERENCE
				ARTERIAL	VENOUS	
1. A.G.	48	Uremia	Semicomatose	0.77	0.88	−0.11
2. R.B.	53	Uremia	Comatose	0.82	0.92	−0.10
3. V.W.	55	Alcoholism	Alert	0.98	0.90	0.08
4. D.G.	42	Nephrosis	Lethargic	0.50	0.53	−0.03
5. D.C.	37	Carcinoma, lung	Alert	0.73	0.97	−0.24
6. J.H.	60	Alcoholism Psychosis	Alert	0.74	0.80	−0.06
7. R.G.	22	Postanoxic coma	Comatose	0.86	0.90	−0.04
8. F.R.	59	Asthma	Alert	0.75	0.73	0.02
9. W.J.	49	Hypertension Uremia	Lethargic	0.80	0.88	−0.08
Average				0.77	0.83	−0.06

Table II gives the arterial and venous blood ammonia levels in nine patients with varying degrees of congestive heart failure, liver enlargement, and states of consciousness. All of the arterial ammonia levels are elevated, with an average of 1.33 gamma/c.c. The arteriovenous difference is consistently positive, i.e., an uptake or removal of ammonia by the tissues. The average venous blood ammonia is 1.06 gamma/c.c., slightly above normal levels. Several of the venous ammonia levels fall within the normal range.

TABLE II. BLOOD AMMONIA LEVELS IN PATIENTS WITH RIGHT-SIDED CONGESTIVE HEART FAILURE

PATIENT	AGE	ETIOLOGIC DIAGNOSIS	MENTAL STATE	BLOOD AMMONIA		A-V DIFFERENCE
				ARTERIAL	VENOUS	
1. F.T.	39	R.H.D.	Lethargic	1.23	1.02	0.21
2. G.B.	32	R.H.D.	Alert, easily fatigued	1.16	0.86	0.30
3. M.J.	54	H.A.S.H.D.	Alert, easily fatigued	1.27	1.07	0.20
4. C.W.	78	A.S.H.D.	Lethargic	1.53	1.23	0.30
5. B.D.	56	R.H.D.	Alert	1.19	0.94	0.25
6. C.H.	36	R.H.D.	Irritable	1.15	0.82	0.33
7. A.S.	49	R.H.D.	Alert, euphoric	1.52	1.28	0.24
8. E.T.	67	E.H.D.	Lethargic	1.25	1.03	0.22
8.(a) E.T.				0.79	0.86	−0.07*
9. V.H.	41	R.H.D.	Semicomatose	1.65	1.25	0.40
Average				1.33	1.06	0.27

R.H.D.—Rheumatic heart disease
A.S.H.D —Arteriosclerotic heart disease
H.A.S.H.D —Hypertensive and arteriosclerotic heart disease
E.H.D —Emphysema heart disease
*Not included in averages. See text for explanation.

Determination 8(a) was excluded from the averages. This was a repeat study on a subject number 8 following a good response to digitalis, mercurial diuretics, and other measures designed to correct the congestive failure. The blood ammonia level returned to normal with restoration of cardiac competence.

DISCUSSION

Hypoxia is the traditional explanation for the cerebral symptoms of chronic congestive heart failure, although recently a cerebral metabolic lesion has been suspected. This is explicit in Stead's statement, "It is probable that the changes in cerebral metabolism caused by heart failure have a mechanism more complex than simple reduction of blood supply to the brain. It seems evident that there must be widespread disorders of intermediary metabolism produced by the decreased blood supply to the liver, endocrine glands, gastrointestinal tract and all other organs of the body. Such lack of proper function of other organs may well have a secondary effect on cerebral metabolism."[13]

One of the outstanding lesions in chronic passive congestion is the altered structure and function of the liver. Hepatic function is consistently impaired in moderate to severe cardiac failure. Of 105 patients studied by Evans and associates,[14] 96 per cent showed elevation of Bromsulphalein retention from six to fifty per cent. The degree of abnormality usually paralleled the severity of the congestive state. Following satisfactory response to therapy, the excretion of Bromsulphalein returned toward normal. In subject 8, Table II, it can be seen that both the arterial and venous ammonia levels returned to normal after therapy, and the arteriovenous difference reverted from positive (+0.22 g./c.c.) to the near zero value (−0.07 g./c.c.) characteristic of normal subjects.

The histopathologic changes found in chronic right-sided heart failure include atrophy and necrosis of the cells around the central vein, central fibrosis, and in chronic and severe failure "cardiac cirrhosis."[15-18] Since the hepatic functional patterns in heart failure and primary liver disease are difficult to differentiate, one might predict a common mechanism for the cerebral symptoms seen in both of these conditions.

The recent literature has emphasized the relation of blood ammonia to the state of consciousness in liver disease.[4-9] These investigators have found elevated blood ammonia levels in patients with liver disease, and several authors have reproduced the neurologic disturbances by the use of a high protein diet, the administration of ammonium chloride, or by other methods of raising blood ammonia.[4,6,7] Bessman and associates,[8] studying hepatic coma, have found marked elevation of the blood ammonia and a positive cerebral arteriovenous difference in contrast to the near zero or negative arteriovenous ammonia difference in subjects with no impairment of liver function. It was further observed that the uptake of ammonia by muscle was approximately the same as the uptake of ammonia by brain, when the blood level of ammonia was elevated.[9] We can, therefore, probably assume that the brain arteriovenous difference was also positive in our patients with elevated blood ammonia and a positive muscle arteriovenous difference.

The cardiac subjects of this investigation showed a moderate elevation of blood ammonia, consistent with their moderate alterations in consciousness. It seems likely that ammonia plays a role in the cerebral alterations seen in cardiac failure in the same manner as it does in hepatic coma. It has been proposed that the mode of action of ammonia in deranged cerebral function is by aminating alpha ketoglutarate, an essential component of the Krebs cycle.[9] Thus by the loss of one component of the cycle upon which the brain depends for energy, cerebral metabolism, and ultimately function, are impaired.

In view of the elevated blood ammonia in cardiac failure, the possibility that overzealous use of ammonium chloride in congestive heart failure may contribute to the lassitude and lethargy of the patient should be considered. The reproducibility of the cerebral disturbances, including coma, of liver disease by the administration of ammonium chloride has been demonstrated by MacDermott and Adams,[4] and Sherlock and associates.[7]

SUMMARY

1. Arterial and venous blood ammonia levels were measured in nine control patients and in nine patients with congestive heart failure.

2. The average arterial and venous ammonia levels of the control patients were 0.79 and 0.83 gamma/c.c., respectively. The average arterial and venous blood ammonia levels of patients with congestive heart failure were 1.33 and 1.06 gamma/c.c., respectively.

3. Patients without liver dysfunction or congestive heart failure show normal blood ammonia values with a negligible arteriovenous difference while patients with congestive heart failure show an elevated blood ammonia with an uptake of ammonia by the tissues.

4. The cerebral manifestations of lassitude, lethargy, and coma seen in congestive heart failure may be due in part to ammonia intoxication, etiologically similar to the cerebral symptoms of hepatic insufficiency.

5. It is suggested that ammonium chloride be used with caution in patients with cardiac failure presenting cerebral manifestations or severe liver dysfunction.

SUMMARIO IN INTERLINGUA

1. Le nivellos venose e arterial de ammoniaco sanguinee esseva mesurate in 9 patientes con congestive dysfunctionamento cardiac e in 9 individuos de controlo.

2. In le individuos de controlo le valores median de ammoniaco sanguinee esseva 0,79 μg per cm cubic in le sanguine arterial e 0,83 μg per cm cubic in le sanguine venose. Le correspondente valores pro le patientes con congestive dysfunctionamento cardiac esseva 1,33 e 1,06.

3. Patientes sin dysfunctionamento hepatic e sin congestive dysfunctionamento cardiac monstra normal nivellos de ammoniaco del sanguine con un negligibile differentia arterio-venose. Patientes con dysfunctionamento congestive del corde monstra un elevate nivello de ammoniaco sanguinee con retention de ammoniaco per le texitos.

4. Le manifestationes cerebral de lassitude, lethargia, e coma que es observate in congestive dysfunctionamento cardiac es possibilemente causate in parte per ammoniotoxicosis. Le etiologia esserea simile a illo del symptomas cerebral observate in insufficientia hepatic.

5. Se impone le conclusion que in patientes de dysfunctionamento cardiac con manifestationes cerebral o con sever dysfunctionamento hepatic, le uso de chlorido de ammonium debe esser regulate cautissimemente.

REFERENCES

1. Friedberg, C. K.: Diseases of the Heart, Philadelphia, 1950, W. B. Saunders Company, p. 145.
2. Altschule, M. D.: Physiology in Diseases of the Heart and Lungs, Cambridge, Mass. 1954, Harvard University Press, p. 192.
3. Zimmerman, H. J.: The Liver in Heart Disease, Nebraska Med. J. **38**:367, 1953.
4. McDermott, W. V., Jr., and Adams, R. D.: Episodic Stupor Associated With an ECK Fistula in the Human With Particular Reference to the Metabolism of Ammonia, J. Clin. Invest. **33**:1, 1954.
5. Seegmiller, J. E., Schwartz, R., and Davidson, C. S.: The Plasma "Ammonia" and Glutamine Content in Patients With Hepatic Coma, J. Clin. Invest. **33**:984, 1954.
6. Phillips, G. B., Schwartz, R., Gabuzda, G. J., Jr., and Davidson, C. S.: The Syndrome of Impending Hepatic Coma in Patients With Cirrhosis of the Liver Given Certain Nitrogenous Substances, New England J. Med. **247**:239, 1952.
7. Sherlock, S., Summerskill, W. H. J., White, L. P., and Phear, E. A.: Portal-Systemic Encephalopathy; Neurological Complications of Liver Disease, Lancet **2**:453, 1954.
8. Bessman, S. P., Fazekas, J. R., and Bessman, A. N.: The Uptake of Ammonia by the Brain in Hepatic Coma, Proc. Soc. Exper. Biol. & Med. **85**:66, 1954.
9. Bessman, S. P., and Bessman, A N.: Cerebral and Peripheral Uptake of Ammonia in Twin Disease With an Hypothesis for the Mechanism of Hepatic Coma, J. Clin. Invest. **34**:622, 1955.
10. Seligson, D., and Seligson, H.: A Microdiffusion Method for the Determination of Nitrogen Liberated as Ammonia, J. Lab. & Clin. Med. **38**:324, 1951.
11. Conway, E. J.: Apparatus for the Micro-Determination of Certain Volatile Substances: The Blood Ammonia With Observations on Normal Human Blood, Biochem. J. **29**:2755, 1935.
12. Seligson, D.: Unpublished Data—Personal communication.
13. Cecil, R. L. (Editor): Text Book of Medicine, ed. 7, Philadelphia, 1947, W. B. Saunders Company, p. 1146.
14. Evans, J. M., Zimmerman, H. J., Wilmer, J. G., Thomas, L. J., and Ethridge, C. B.: Altered Liver Function of Chronic Congestive Heart Failure, Am. J. Med. **13**:704, 1952.
15. Kotin, P., and Hall, E. M.: "Cardiac" or Congestive Cirrhosis of the Liver, Am. J. Path. **27**:561, 1951.
16. Katzin, H. M., Waller, J. V., and Blumgart, H. L.: "Cardiac Cirrhosis" of the Liver; Clinical and Pathological Study, Arch. Int. Med. **64**:457, 1939.
17. Koletsky, S., and Barnebee, J. H.: "Cardiac" or Congestive Cirrhosis; Pathologic and Clinical Aspects, Am. J. M. Sc. **207**:421, 1944.
18. Sherlock, S.: The Liver in Heart Failure; Relation of Anatomical, Functional and Circulatory Changes, Brit. Heart J. **13**:273, 1951.

OBSERVATIONS ON THE EFFECT OF TETRAETHYLAMMONIUM CHLORIDE ON THE PULMONARY VASCULAR RESISTANCE IN MITRAL STENOSIS

RALPH C. SCOTT, M.D., SAMUEL KAPLAN, M.D., AND WILLIAM J. STILES, M.D.

CINCINNATI, OHIO

TETRAETHYLAMMONIUM chloride (TEAC) has been demonstrated to lower pulmonary artery pressure and pulmonary vascular resistance in some patients with pulmonary hypertension (secondary to left ventricular failure and to chronic lung disease).[1] These findings suggest that in certain cases of pulmonary hypertension at least one component of the increased pulmonary vascular resistance is mediated through the autonomic nervous system.[1]

Patients with mitral stenosis usually have elevated pulmonary vascular resistances.[2-11] The exact manner in which this increase in pulmonary resistance is brought about is obscure.[3,7,11,12] It is probably due to both organic vascular changes[11,13-16] and vasoconstriction[2-4,8,17,18] in the pulmonary bed.

The present investigation was undertaken in order to study the effect of TEAC on the pulmonary artery pressure and pulmonary vascular resistance in patients with mitral stenosis.

METHODS AND MATERIALS

Thirty-nine patients with mitral stenosis have undergone cardiac catheterization in the Cardiac Laboratory at the Cincinnati General Hospital during the past four years. Results of some of these studies have been previously reported.[5,19a,b]

The present report is concerned with the hemodynamic findings in six of these patients before and after the administration of TEAC and again in two patients before and after TEAC following mitral valvulotomy.

Cardiac catheterization was carried out according to the method of Cournand and Ranges.[20] The patients were not given sedation. The procedure was performed in the morning after a light breakfast. Continuous observation of the patient's electrocardiogram was made throughout the procedure. Pulmonary "capillary" pressures were obtained by the method of Hellems and associates.[21] A blood sample was obtained (in all cases except one) from the catheter tip in this position. The catheter was then withdrawn

From the Cardiac Laboratory, Cincinnati General Hospital, and the Department of Interna Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Received for publication April 6, 1955.

to the main pulmonary artery under fluoroscopic control. The pulmonary artery and the brachial artery pressures were then measured. All pressures were taken with Hathaway variable impedance gauges and recorded on the Hathaway optical oscillograph. Cardiac outputs were determined by the direct Fick method. The patient's expired air was collected in a Douglas bag for a timed period of two minutes. During the collection, simultaneous blood samples were obtained from the pulmonary artery and the brachial artery under oil during a timed interval of 30 seconds.

The blood samples were analyzed for carbon dioxide and oxygen by the method of Van Slyke and Neill.[22] Duplicate samples were required to check within 0.2 volume per cent. Expired air was measured in a Tissot spirometer and was analyzed either in the Beckman oxygen analyzer or by the Scholander microgas technique. With the latter method duplicate samples were required to check within 0.03 volume per cent.

Under fluoroscopic control the catheter was again advanced into a branch of the pulmonary artery as far as possible so that the branch was occluded. The pulmonary "capillary" pressure was again recorded. Then 5 mg. of TEAC per kilogram of body weight was injected into the catheter in a period of 30 seconds. When a maximal effect was noted (increased pulse rate, sensation of tingling around the mouth, fall in brachial artery pressure), usually within about five minutes, the pulmonary "capillary" pressure was recorded. Then the catheter was immediately withdrawn to the pulmonary artery and its pressure recorded. A second cardiac output, exactly as the first, was promptly carried out. The brachial artery pressure was recorded immediately after the second cardiac output.

Mean pulmonary artery, brachial artery, and pulmonary "capillary" pressures were determined by planimetric integration over at least two respiratory cycles. Pressures recorded through the catheter were corrected for the measured level of the gauges, using 10 cm. above the fluoroscopic table as the arbitrary zero point.[17]

Pulmonary "arteriolar"* resistance[2] was calculated according to the formula:†

$$R = \frac{PA_m - \text{"PC"}_m}{CO} \times 1{,}332 \text{ dynes seconds cm.}^{-5}$$

Total pulmonary resistance[2] was calculated as follows:†

$$R' = \frac{PA_m}{CO} \times 1{,}332 \text{ dynes seconds cm.}^{-5}$$

*The term pulmonary "arteriolar" resistance, as has been emphasized in previous reports,[17,29] is used in the physiologic sense to designate small vessels between the large branches of the pulmonary artery and the true pulmonary capillaries. In order to try to avoid controversy in terminology we shall for the most part in this paper use the general term pulmonary "vascular" resistance rather than pulmonary "arteriolar" resistance.

†These formulas have been criticized recently as not being correct.[30,31] However, it has also been pointed out that although the results so obtained from them are crude, they do serve a useful purpose in estimating the severity of augmented pulmonary or mitral valve resistances.[32] Furthermore, these same formulas have been used extensively in previous physiologic studies in mitral valve disease.[2,3,5,7-9,18] Until better formulas are devised we shall employ them, being fully aware that the results they give are not absolute but only relative.

Total peripheral resistance[2] was calculated as follows:

$$R'' = \frac{BA_m}{CO} \times 1{,}332 \text{ dynes seconds cm.}^{-5}$$

Where PA_m = pulmonary arterial mean pressure in mm. Hg
"PC" = pulmonary "capillary" mean pressure in mm. Hg
BA_m = brachial arterial mean pressure in mm. Hg
CO = cardiac output, c.c. per second
1,332 = conversion factor from mm. Hg to dynes per cm.^{2}

Mitral valve orifice areas were calculated according to the hydraulic formula* of Gorlin and Gorlin.[23]

Variations in cardiac output were considered significant if the change was 10 per cent or greater.[1] A change greater than ±10 mm. Hg for the pulmonary artery mean pressure or ±5 mm. Hg for the pulmonary "capillary" pressure was considered significant.[29]

Four of these six patients subsequently had mitral valvulotomy. All had excellent results and were able to return to work. Two of these patients have had cardiac catheterization performed again after surgery and have had the study with TEAC repeated (four months after mitral valvulotomy in the case of P.L., and two months after mitral valvulotomy in the case of W.S.). The other two have refused repeat cardiac catheterization.

RESULTS

Part I. Patients Studied Before Surgery (Table I).—

Mean pulmonary artery pressure: All six patients studied had pulmonary hypertension, and the mean pulmonary artery pressure was lowered to a significant degree by TEAC in five of the six.

In two cases (S.C., C.McC.) the fall was due to a decline in cardiac output, and in three (H.S., P.L., W.S.) the fall was due to a decrease in pulmonary vascular resistance.

Pulmonary vascular resistance: Pulmonary vascular resistance showed a significant decrease (a change of 10 per cent or greater[1]) after TEAC in three patients, reaching a normal value in one (H.S.). There was a significant increase in one patient (A.T.) and no significant change in two.

Pulmonary "capillary" pressure: The pulmonary "capillary" pressure declined with TEAC in three patients and remained essentially unchanged in the remaining three.

Cardiac output: A change in cardiac output of 10 per cent or greater was considered significant.[1] Three showed a significant decrease after TEAC, and three showed an increase.

Mean brachial artery pressure and peripheral resistance: The mean brachial artery pressure was lowered more than 10 mm. in three patients after TEAC; in one this was a result of a decline in cardiac output, in one to a concomitant decline in cardiac output and peripheral resistance, and in one to a decline in peripheral resistance.

---

*See footnote at bottom of page 721.

TABLE I. HEMODYNAMIC EFFECTS OF TETRAETHYLAMMONIUM CHLORIDE ON PATIENTS WITH MITRAL STENOSIS

SUBJECT	PERIOD*	PRESSURES (MM. HG)							CARDIAC OUTPUT		PULMONARY VASCULAR RESISTANCE		TOTAL PULMONARY RESISTANCE		TOTAL PERIPHERAL RESISTANCE	
AGE, RACE, SEX		R A	P A S/D	P A MEAN	"P C"	PA-"PC" GRADIENT	B A S/D	B A MEAN	L./MIN.	% CHANGE	DYNES/SEC./CM.$^{-5}$	% CHANGE	DYNES/SEC./CM.$^{-5}$	% CHANGE	DYNES/SEC./CM.$^{-5}$	% CHANGE
1. S. C.	1	—	72/46	64	38	26	138/82	100	5.47		380		935		1455	
52 W.M.	2	5	52/26	39	22	17	105/68	83	3.93	−28	346	−9	793	−15.2	1688	+16
2. A. T.	1	—	54/34	42	17	25	110/62	81	4.47		447		751		1448	
44 W.M.	2	9	45/22	37	8	29	80/45	61	3.83	−14	605	+35	772	+ 2.8	1273	−12
3. H. S.	1	8	68/46	51	22	29	114/73	84	6.29		368		648		1067	
31 W.F.	2	6	34/23	29	21	8	86/48	66	7.08	+13	90	−76	327	−49.5	745	−30
4. C. McC.	1	—	92/47	70	20	50	138/61	88	8.88		452		630		791	
26 C.M.	2	11	72/38	50	19	31	139/74	99	5.51	−38	439	− 3	721	+14.4	1431	+81
5. P. L.	1	—	92/44	65	26	39	96/51	68	3.62		861		1435		1501	
41 C.M.	2	3	72/36	47	29	18	76/56	66	4.13	+14	348	−60	910	−36.6	1277	−15
	3	—	48/24	38	16	22	106/48	70	5.18		339		586		1080	
	4	8	33/17	23	14	9	104/64	79	5.23	+ 1	138	−59	351	−40.1	1207	+12
6. W. S.	1	—	142/76	97	44	53	105/60	74	4.24		999		1828		1385	
34 W.M.	2	4	118/66	84	35	49	90/50	66	4.76	+12	823	−18	1410	−22.9	1108	−20
	3	12	92/58	71	28	43	126/75	106	6.28		542		904		1355	
	4	10	62/42	52	27	25	108/88	97	6.64	+ 6	301	−45	623	−31.1	1168	−14

*Period 1 = Control observations; 2 = Observations after TEAC; 3 = Control observations after mitral valvulotomy; 4 = Observations after TEAC after mitral valvulotomy.

R A = Right atrium; P A = Pulmonary artery; "P C" = Pulmonary "capillary"; B A = Brachial artery.

Part II. Patients Studied After Surgery (Table I).—

Mean pulmonary artery pressure: The mean pulmonary artery pressure was lowered after surgery to a significant degree in both patients (to a value lower than that obtained with TEAC in Part I of the study). It declined even further with TEAC. This decline was due to a fall in pulmonary vascular resistance in both cases.

Pulmonary vascular resistance: The pulmonary vascular resistance was lowered in both patients after surgery (to a value lower than that obtained after TEAC administration in Part I). This resistance fell further with TEAC, even reaching a normal value in one patient (P.L.).

Pulmonary "capillary" pressure: The pulmonary "capillary" pressure was lowered in both patients after surgery. It showed no significant change with TEAC administration.

Cardiac output: There was a significant increase in cardiac output in both patients after mitral valvulotomy. There was no significant change in cardiac output after the administration of TEAC.

Mean brachial artery pressure and peripheral resistance: The mean brachial artery pressure after TEAC showed no appreciable change. The peripheral resistance after TEAC rose in Case 5 and fell in Case 6.

Part III. General Observations.—The respiratory quotient (R.Q.) was determined in three patients (C.McC., P.L., W.S.).* The R.Q. in these three before and after TEAC satisfied the criteria of Fishman and associates[33] for the steady state (a change of not more than 0.11). The oxygen consumption also satisfied the criteria of Fishman and associates[33] for the steady state (a change of not more than +11 per cent) in seven of the eight determinations (Table II). In the other one the change was only slightly greater than +11 per cent (+12 per cent). Thus all of our cases either were in the steady state or nearly approached it.

The arterial oxygen saturation fell after administration of TEAC in all except one patient (Table II). The cause for this change is not apparent. In two cases (H.S., P.L.) the arterial oxygen saturation declined to significant hypoxic levels (less than 85 per cent saturation),[25,34] yet the pulmonary artery pressure did not rise.

The pulmonary "capillary" blood sample was obtained in five patients. The saturation ranged from 97.9 to 100 per cent, exceeding the brachial artery oxygen saturation in each instance (Table II).

The number of patients in this study is too small to submit the results to statistical analysis. Nevertheless the trend is such that it appears that if the series were larger the fall in pulmonary artery pressure and pulmonary vascular resistance after TEAC would probably be significant statistically.

---

*In the other three the R.Q. could not be calculated since the expired air was analyzed in the Beckman oxygen analyzer, and no carbon dioxide analysis was done.

TABLE II. PHYSIOLOGIC DATA ON PATIENTS WITH MITRAL STENOSIS GIVEN TETRAETHYLAMMONIUM CHLORIDE

SUBJECT AGE, RACE, SEX	PERIOD*	OXYGEN CONSUMPTION		OXYGEN SATURATION (% CAPACITY)		HEART RATE (BEATS/MIN.)	A-V OXYGEN DIFF. (VOL. %)	MITRAL VALVE AREA ($CM.^2$)	BODY SURFACE AREA ($M.^2$)
		C.C./MIN./$M.^2$	% CHANGE	B A	"P C"				
1. S. C. 52 W.M.	1	162		90.8	99.5	98	5.67	—†	1.91
	2	137	−15	88.9	—	137	6.67		
2. A.T. 44 W.M.	1	109		95.9	97.9	80	4.32	0.3	1.78
	2	116	+6	93.3	—	116	5.38		
3. H. S. 31 W.F.	1	137		85.7	98.7	96	3.56	1.4‡	1.64
	2	154	+12	83.9	—	85	3.56		
4. C. McC. 26 C.M.	1	193		89.7	100.0	98	3.67	2.6	1.69
	2	179	−7	96.3	—	90	5.48		
5. P. L. 41 C.M.	1	133		88.1	98.3	110	6.61	0.9‡	1.80
	2	138	+4	82.8	—	138	6.03		
	3	148		94.0	99.5	83	5.12	2.1§	
	4	156	+5	91.5	—	100	5.35		
6. W. S. 34 W.M.	1	193		95.4	—	98	6.88	0.8‡	1.57
	2	191	−1	89.2		116	6.05		
	3	189		93.8		109	4.71	2.8§	
	4	195	+3	87.0	—	143	4.61		

*Same as Table I.
†This patient had some mitral insufficiency and the forward area of the mitral valve was not measured.
‡Size of mitral valve orifice estimated at time of surgery before valvulotomy.
§Size of mitral valve orifice estimated at time of surgery after mitral valvulotomy.
B A = Sample withdrawn from brachial artery; "P C" = Sample withdrawn from catheter tip wedged in branch of pulmonary artery.

DISCUSSION

In mitral stenosis the stenotic valve orifice offers obstruction to the flow of blood from the left atrium into the left ventricle. As the left atrial pressure rises this is reflected in an increase in pressure in the pulmonary veins, capillaries, and arteries.[3,26] If the pressure in the pulmonary capillaries is elevated above the colloid osmotic pressure of plasma (25 to 30 mm. Hg) for any considerable length of time pulmonary edema may ensue.[2,3] Apparently as a protective device to forestall such an event there develops an increase in the pulmonary arteriolar* (vascular) resistance.[2,3,17] It has been pointed out that this increased vascular resistance is a physiologic counterpart of the anatomic changes that have been observed in the small pulmonary arteries.[3]

The anatomic changes in the small pulmonary arteries and arterioles†

*Objection has been raised by Araujo and Lukas[9] to this teleologic explanation of the increase in pulmonary arteriolar resistance.

†The term "arteriole" is controversial, some workers[17] stating that there are no true arterioles in the lung while others avoid the use of the term "arteriole" in their descriptions of the vascular structure of the lung.[35-37] Other authorities[11,13-15,38] indicate that there are vessels in the lung that have histologic characteristics similar to arterioles in the systemic circuit. We shall henceforth use the term "arteriole" in this paper to refer to the small radicles of the pulmonary arterial tree.

in patients with mitral stenosis have been well described.[11,13-16] The considerable reduction in pulmonary vascular resistance found in many patients after mitral valve surgery suggests that at least some of the increased vascular resistance may be on the basis of vasoconstriction and thus be at least partly reversible.[4,8,10,26,27,38] Other workers[14,39,40] have suggested that some of the actual organic vascular changes (such as medial hypertrophy) may reverse in time after mitral valvulotomy. The time required for such reversal has been estimated to take from three to six months for the patients with the so-called "low gradient" (low pulmonary "capillary"-pulmonary artery pressure gradient) and as long as two or more years for those with severe changes.[40,41]

As has been emphasized[7,18] the nature and reversibility of the increased pulmonary vascular resistance are important in respect to mitral valve surgery. If the anatomic or functional changes are not improved after mitral valvulotomy, the patient may remain severely handicapped. Therefore some means of predicting preoperatively if any of the vascular resistance is reversible is highly desirable.

If the increase in pulmonary vascular resistance is presumed to be due to both vasoconstriction and organic changes, release of the vasomotor control should permit the assessment of what portion of the increased resistance is due to the organic changes. If this should be the case it might be possible to predict preoperatively in a given patient with mitral stenosis at least the minimum benefit he might anticipate from surgery. In other words, by the use of an autonomic blocking agent such as TEAC the neural component of the increased vascular resistance should be largely inhibited. Then those cases whose resistance remained high (and not due to a significant change in cardiac output) might be the ones with advanced vascular changes.

Unfortunately the problem is probably not so simply resolved. In the first place other factors such as anoxia[12,24,26,29,42,43] may have a direct action on the pulmonary vascular bed to produce vasoconstriction, and thus not be mediated by the autonomic nervous system. Secondly, it has also been demonstrated that there occasionally is no good correlation between the degree of elevation of pulmonary vascular resistance and the extent of the organic vascular changes.[16,44] It is probable, however, as pointed out by Goyette and associates,[16] and also by Denst and co-workers,[11] that the increased pulmonary resistance in those patients who showed little or no vascular changes on lung biopsy may have been due to vasoconstrictor activity.

Despite these obstacles it was hoped that the use of TEAC might shed some further light on the problem of the nature of the increased pulmonary vascular resistance in patients with mitral stenosis. We are fully aware of the criticisms of the use of the pulmonary "capillary" pressure as a reflection of left atrial pressure.[30,32,45a,b] But as more evidence is presented it appears that technically satisfactory tracings may be reasonably reliable.[32,46-49]

There is an inverse relationship between the pulmonary vascular resistance and cardiac output and a direct relationship between pulmonary vascular resistance and the pulmonary artery-pulmonary "capillary" gradient. Thus, either an increase in cardiac output or a fall in the gradient will result in a decline

in the calculated pulmonary vascular resistance. However, the degree of increase of cardiac output in Cases 3, 5, and 6 in Part I is insufficient alone to account for the magnitude of the decline of pulmonary vascular resistance. In fact, if we assume that resistance to flow is due entirely to a diminution in the cross-sectional area of the pulmonary vascular bed secondary to organic changes, then an increase in cardiac output would result in an increase rather than a fall in pulmonary artery pressure. The observed results in these three cases can be best explained on the basis of some primary decrease in pulmonary vascular resistance (presumably a decrease in vasoconstrictor tone).

We have thus found that at least in some cases of mitral stenosis a portion of the increased pulmonary vascular resistance is mediated through the autonomic nervous system. This has already been demonstrated in certain cases of pulmonary hypertension secondary to left-heart failure and to chronic lung disease.[1] Our findings in cases of mitral stenosis are also in agreement with those of Halmágyi and co-workers.[43]

The present study certainly is too limited in scope to draw any definitive conclusions. It is suggested, however, that a significant fall in pulmonary artery pressure secondary to a decline in pulmonary vascular resistance after TEAC administration in a patient with mitral stenosis preoperatively is a good prognostic sign. In both of our cases studied before and after surgery, the drop in pulmonary artery pressure and pulmonary vascular resistance obtained during the first study with TEAC approached but did not exceed that obtained following mitral valvulotomy. It is of interest that both of these patients have obtained excellent surgical results. Both have been able to return to work and are asymptomatic.*

At the present time it is more difficult to speculate regarding the postoperative results of those cases who do not get a decline in their pulmonary vascular resistance after TEAC. In the present study three such cases were encountered but in all there was a significant fall in cardiac output. One of these cases (A.T.) had excellent results following mitral valvulotomy; the other two have not had surgery.

Further study will be necessary to assess the value of TEAC in predicting preoperatively in patients with mitral stenosis what portion of the increased vascular resistance is reversible.

SUMMARY

1. The effect of tetraethylammonium chloride (TEAC) on the pulmonary artery pressure, pulmonary vascular resistance, and cardiac output was studied in six patients with mitral stenosis.

2. The administration of TEAC produced a significant lowering of mean pulmonary artery pressure in five of six cases. This was due to a decrease in cardiac output in two cases and to a decline in pulmonary vascular resistance in three.

---

*The period of follow-up since the date of surgery on these two patients has been approximately eight months for each.

3. These results suggest that at least in some cases of mitral stenosis a portion of the increase in pulmonary vascular resistance is mediated through the autonomic nervous system.

4. Two of these patients were also studied after mitral valvulotomy. The mean pulmonary artery pressure and the pulmonary vascular resistance were found to be lowered in both patients after surgery (to a value lower than that obtained with TEAC before surgery). The pulmonary artery pressure and pulmonary vascular resistance fell even further in both patients after TEAC.

5. Further study will be necessary to assess the value of TEAC in predicting preoperatively in patients with mitral stenosis what portion of the increased vascular resistance is reversible.

SUMMARIO IN INTERLINGUA

Le presente reporto es concernite con le constatationes hemodynamic in 6 patientes con stenosis mitral qui esseva subjicite a catheterisation cardiac e qui recipeva chlorido de tetraethylammonium in un dose de 5 mg per kg de peso corporee. In 5 del 6 casos le administration del droga resultava in un significative reduction del pression median del arterias pulmonar. Isto esseva causate in 2 casos per un reduction del rendimento cardiac e in 3 casos per un diminuite resistentia del arteriolas pulmonar. In 2 del casos le studio esseva continuate post valvulotomia mitral. Il esseva constatate que in ambe casos le valores median del pression pulmono-arterial e del resistentia pulmono-arteriolar habeva descendite—sin le adjuta del droga—a nivellos infra illos previemente obtenite con le adjuta de chlorido de tetraethylammonium. In plus, in ambe iste patientes le uso del droga post valvulotomia mitral resultava in un reduction additional del pression pulmono-arterial e del resistentia pulmono-arteriolar. Iste observationes pare indicar que al minus in certe casos de stenosis mitral un parte del augmento in resistentia pulmono-arteriolar es mediate via le autonome systema nervose.

The authors wish to thank Doctors Robert A. Helm and Isom C. Walker, Jr., for their valuable assistance.

Mitral valve surgery was performed by Dr. James A. Helmsworth on patients A.T., P.L., and W.S., and by Dr. Aaron I. Grollman on patient H.S.

We were privileged to study patient A.T. through the kind permission of Dr. Harold Kotte and patient H.S. through the kind permission of Dr. Arnold Iglauer.

REFERENCES

1. Fowler, N. O., Westcott, R. N., Hauenstein, V. D., Scott, R. C., and McGuire, J.: Observations on Autonomic Participation in Pulmonary Arteriolar Resistance in Man, J. Clin. Invest. **29**:1387, 1950.
2. Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Studies of the Circulatory Dynamics in Mitral Stenosis. II. Altered Dynamics at Rest, Am. Heart J. **41**:30, 1951.
3. Lewis, B. M., Gorlin, R., Houssay, H. E. J., Haynes, F. W., and Dexter, L.: Clinical and Physiological Correlations in Patients With Mitral Stenosis, V. Am. Heart J. **43**:2, 1952.
4. Draper, A., Heimbecker, R., Daley, R., Carroll, D., Mudd, G., Wells, R., Falholt, W., Andrus, E. C., and Bing, R. J.: Physiologic Studies in Mitral Valvular Disease, Circulation **3**:531, 1951.
5. Scott, R. C., Kaplan, S., and Fowler, N. O.: Physiologic Measurements in Mitral Valve Disease, J. Lab. & Clin. Med. **42**:950, 1953.

6. Eliasch, H., Wade, G., and Werkö, L.: The Effects of Work on the Pulmonary Circulation in Mitral Stenosis, Circulation **5**:271, 1952.
7. Lukas, D. S., and Dotter, C. T.: Modifications of the Pulmonary Circulation in Mitral Stenosis, Am. J. Med. **12**:639, 1952.
8. Taquini, A. C., Donaldson, R. J., Ballina, E. S., D'aiutalo, R. E. H., and Lozada, B. B.: Physiologic Studies in Mitral Stenosis, Am. Heart J. **45**:691, 1953.
9. Araujo, J., and Lukas, D. S.: Interrelationships Among Pulmonary "Capillary" Pressure, Blood Flow and Valve Size in Mitral Stenosis. The Limited Regulatory Effects of the Pulmonary Vascular Resistance, J. Clin. Invest. **31**:1082, 1952.
10. Werkö, L., Biörck, G., Crafoord, C., Wulff, H., Krook, H., and Eliasch, H.: Pulmonary Circulatory Dynamics in Mitral Stenosis Before and After Commissurotomy, Am. Heart J. **45**:477, 1953.
11. Denst, J., Edwards, A., Neuberger, K. T., and Blount, S. G.: Biopsies of the Lung and Atrial Appendages in Mitral Stenosis: Correlation of Data From Cardiac Catheterization With Pulmonary Vascular Lesions, Am. Heart J. **48**:506, 1954.
12. McGregor, M., Bothwell, T. H., Zion, M. M., and Bradlow, B. A.: The Effects of Oxygen Breathing on the Pulmonary Circulation in Mitral Stenosis, Am. Heart J. **46**:187, 1953.
13. Parker, F., Jr., and Weiss, S.: The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, Am. J. Path. **12**:573, 1936.
14. Larrabee, W. F., Parker, R. L., and Edwards, J. E.: Pathology of Intrapulmonary Arteries and Arterioles in Mitral Stenosis, Proc. Staff Meet., Mayo Clin. **24**:316, 1949.
15. Henry, E. W.: The Small Pulmonary Vessels in Mitral Stenosis, Brit. Heart J. **14**:406, 1952.
16. Goyette, E. M., Farinacci, C. J., Forsee, J. H., and Blake, H. A.: The Clinico-Pathologic Correlation of Lung Biopsies in Mitral Stenosis, Am. Heart J. **47**:645, 1954.
17. Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., and Hellems, H. K.: Studies of the Pulmonary Circulation in Man at Rest. Normal Variations and the Interrelations Between Increased Pulmonary Blood Flow, Elevated Pulmonary Arterial Pressure and High Pulmonary "Capillary" Pressure, J. Clin. Invest. **29**:602, 1950.
18. Gorlin, R., Sawyer, C. G., Haynes, F. W., Goodale, W. T., and Dexter, L.: Effects of Exercise on Circulatory Dynamics in Mitral Stenosis, III, Am. Heart J. **41**:192, 1951.
19. (a) Scott, R. C., and Kaplan, S.: The Electrocardiogram in Mitral Valve Disease, J. Lab. & Clin. Med. **42**:950, 1953.
(b) Scott, R. C., Kaplan, S., Fowler, N. O., Jr., and Stiles, W. J.: The Electrocardiographic Pattern of Right Ventricular Hypertrophy in Mitral Valve Disease, Circulation **11**:761, 1955.
20. Cournand, A., and Ranges, H. A.: Catheterization of the Right Auricle in Man, Proc. Soc. Exper. Biol. & Med. **46**:462, 1941.
21. Hellems, H. K., Haynes, F. W., and Dexter, L.: Pulmonary "Capillary" Pressure in Man, J. Appl. Physiol. **2**:24, 1949.
22. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, vol. 2, Baltimore, 1943, Williams and Wilkins Company.
23. Gorlin, R., and Gorlin, S. G.: Hydraulic Formula for Calculation of the Area of the Stenotic Mitral Valve, Other Cardiac Valves, and Central Circulatory Shunts, I. Am. Heart J. **41**:1, 1951.
24. Doyle, J. T., Wilson, J. S., and Warren, J. V.: The Pulmonary Vascular Response to Short-Term Hypoxia in Human Subjects, Circulation **5**:263, 1952.
25. Dexter, L., Whittenberger, J. L., Gorlin, R., Lewis, B. M., Haynes, F. W., and Spiegl, R. J.: The Effect of Chronic Pulmonary Disease (Cor Pulmonale and Hypoxia) on the Dynamics of the Circulation in Man, Tr. A. Am. Physicians **64**:226, 1951.
26. Yu, P. N. G., Simpson, J. H., Lovejoy, F. W., Jr., Joos, H. A., and Nye, R. E., Jr.: Studies of Pulmonary Hypertension. IV. Pulmonary Circulatory Dynamics in Patients With Mitral Stenosis at Rest, Am. Heart J. **47**:330, 1954.
27. Dexter, L.: Pathologic Physiology of Mitral Stenosis and Its Surgical Implications, Bull. New York Acad. Med. **28**:90, 1952.
28. Dexter, L., Gorlin, R., Lewis, B. M., Haynes, F. W., and Harken, D. E.: Physiologic Evaluation of Patients With Mitral Stenosis Before and After Valvuloplasty, Tr. Am. Clin. & Climat. A. **62**:170, 1951.
29. Westcott, R. N., Fowler, N. O., Scott, R. C., Hauenstein, V. D., and McGuire, J.: Anoxia and Human Pulmonary Vascular Resistance, J. Clin. Invest. **30**:957, 1951.
30. Burton, A. C.: Peripheral Circulation, Ann. Rev. Physiol. **15**:213, 1953.
31. Fishman, A. P., and Cournand, A.: Heart, Ann. Rev. Physiol. **15**:247, 1953.
32. Editorial: Pulmonary Wedged Catheter Pressures, Circulation Res. **1**:371, 1953.
33. Fishman, A. P., McClement, J., Himmelstein, A., and Cournand, A.: Effects of Acute Anoxia on the Circulation and Respiration in Patients With Chronic Pulmonary Disease Studied During the "Steady State," J. Clin. Invest. **31**:770, 1952.

34. Cournand, A.: Some Aspects of the Pulmonary Circulation in Normal Man and in Chronic Cardiopulmonary Diseases, Circulation **2**:641, 1950.
35. Miller, W. S.: The Lung, ed. 2, Springfield, Illinois, 1947, Charles C Thomas, Publisher.
36. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 6, Philadelphia, 1952, W. B. Saunders Company.
37. Ham, A. W.: Histology, ed. 2, Philadelphia, 1953, J. B. Lippincott Company.
38. Gall, E. A.: Personal communication.
39. Carlotti, J., Joly, F., Sicot, J. R., Voci, G., and Cazals, F.: Étude Physio-Pathologique de la Petite Circulation au Cours due Rétrécissement Mitral (Travail Basé sur 50 Cas), Arch. mal. coeur V **45**:412, 1952.
40. Mudd, J. G., Kistner, W. F., Hanlon, C. R.: The Course of Pulmonary Hypertension After Surgical Treatment of Mitral Stenosis, Official Program, Part II, Second World Congress of Cardiology, p. 140.
41. Carlotti, J., Soulie, P., Joly, F., Sicot, J. R., and Degeorges, M.: Postoperative Hemodynamic Studies Carried Out in 48 Cases of Mitral Stenosis, Official Program, Part II, Second World Congress of Cardiology, p. 109.
42. Fowler, N. O., Cubberly, R., and Dorney, E.: Pulmonary Blood Distribution and Oxygen Diffusion in Mitral Stenosis, AM. HEART J. **48**:1, 1954.
43. Halmágyi, D., Felkai, B., Iványi, J., Zsótér, T., Tényi, M., Szücs, Zs.: The Role of the Nervous System in the Maintenance of Pulmonary Arterial Hypertension in Heart Failure, Brit. Heart J. **15**:15, 1953.
44. Edwards, J. E., Tompkins, R. G., Hood, R. T., Jr., Kirklin, J. W., and Burchell, H. B.: Biopsy of the Lung and Cardiac Catheterization Studies in Patients Treated Surgically for Mitral Stenosis, J. Lab. & Clin. Med. **40**:795, 1952.
45. (a) Ankeney, J. L.: Interrelations of Pulmonary Arterial, "Capillary," and Left Atrial Pressures Under Experimental Conditions, Am. J. Physiol. **169**:40, 1952.
(b) Ankeney, J. L.: Further Experimental Evidence That Pulmonary Capillary Pressures do not Reflect Cyclic Changes in Left Atrial Pressure, Circulation Res. **1**:58, 1953.
46. (a) Connolly, D. C., Lev, R., Kirklin, J. W., and Wood, E. H.: Pulmonary Artery Wedge Pressures in Mitral Valve Diseases; Relationship to Left Atrial Pressure, Fed. Proc. **12**:28, 1953.
(b) Connolly, D. C., Tompkins, R. G., Lev, R., Kirklin, J. W., and Wood, E. H.: Pulmonary Artery Wedge Pressures in Mitral Valve Disease; Relationship to Left Atrial Pressure, Proc. Staff Meet., Mayo Clin. **28**:72, 1953.
(c) Connolly, D. C., Kirklin, J. W., and Wood, E. H.: The Relationship Between Pulmonary Artery Wedge Pressure and Left Atrial Pressure in Man, Circulation Res. **2**:434, 1954.
47. (a) Werkö, L., Varnauskas, E., Eliasch, H., Lagerlöf, H., Senning, A., and Thomasson, B.: Further Evidence That the Pulmonary Capillary Venous Pressure Pulse in Man Reflects Cyclic Pressure Changes in the Left Auricle, Circulation Res. **1**:337, 1953.
(b) Werkö, L., Varnauskas, E., Eliasch, H., and Thomasson, B.: The Influence of the Pulmonary Arterial Pressure on the Pulmonary Capillary Venous Pressure in Man, Circulation Res. **1**:340, 1953.
48. Björk, V. O., Malmström, G., and Uggla, L. C.: Left Atrial and Pulmonary "Capillary" Pressure Curves During Valsalva's Experiment, AM. HEART J. **47**:635, 1954.
49. Epps, R. G., and Adler, R. H.: Left Atrial and Pulmonary Capillary Venous Pressures in Mitral Stenosis, Brit. Heart J. **15**:298, 1953.

AURICULAR FLUTTER: A HEMODYNAMIC BASIS OF CLINICAL FEATURES

MALCOLM C. MCCORD, M.D., AND S. GILBERT BLOUNT, JR., M.D.

DENVER, COLO.

CLINICIANS have been aware for many years of the occurrence of rapid neck vein pulsations in patients with auricular flutter.[1] Auscultatory phenomena peculiar to this cardiac arrhythmia have also been well described in the past.[2] These physical findings have been emphasized primarily as aids in the bedside detection of auricular flutter with little attention devoted to the value of these signs in appraising the underlying dynamic state of the cardiovascular system.

An investigation has been carried out in this laboratory regarding the basic hemodynamic characteristics of auricular contraction during flutter by an analysis of data obtained by right-heart catheterization in patients with this arrhythmia and with other types of auricular arrhythmias. An attempt has been made to determine the factors responsible for the development of the classical physical findings so that the clinical value of these signs may be extended.

Observations are presented on three representative patients with auricular flutter and on one patient with a supraventricular tachycardia.

MATERIAL AND METHODS

Right-heart catheterization was carried out in the usual manner. Pressures were determined using Statham strain gauges and a Hathaway recording apparatus. The zero point of reference was 10 cm. above the table with the patient supine. Auricular pressure tracings were obtained in six patients with auricular flutter, eleven patients with a supraventricular tachycardia, and in thirty-four patients with auricular fibrillation. Detailed presentation is given of three of the patients with auricular flutter as these patients exhibited varying clinical manifestation of the arrhythmia. One of the patients with a supraventricular tachycardia is presented for comparison.

CASE REPORTS

CASE 1.—H. K., a 21-year-old man had rheumatic fever at ten years of age and was noted to have valvular heart disease at that time. Progressively severe exertional dyspnea and ease

From the Cardiovascular Laboratory and Department of Medicine, The University of Colorado School of Medicine, Denver, Colo.

This study was supported by a United States Public Health Service Research Grant H-1208.

Received for publication April 13, 1955.

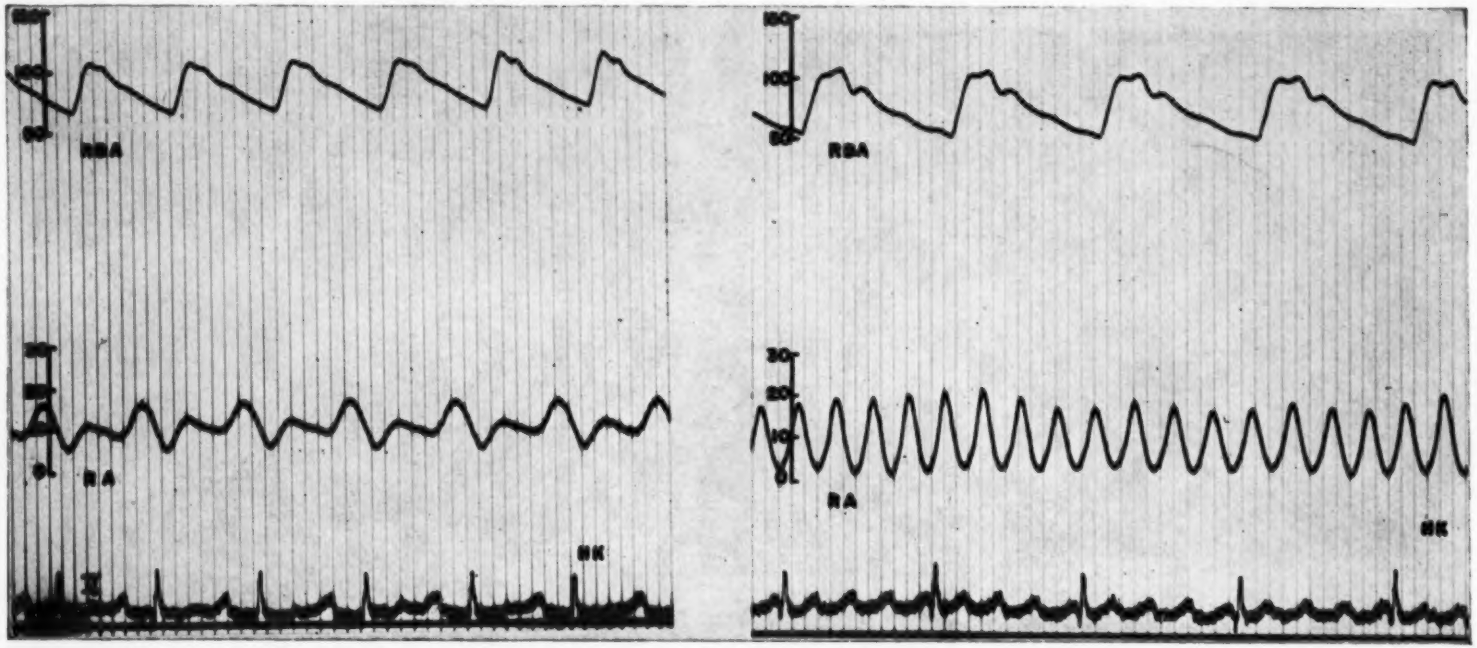


Fig. 1.—Case 1. The pressure tracing to the left demonstrates the right auricular pressure, *RA*, during sinus rhythm, showing high amplitude *a* waves. The right auricular pressure during auricular flutter is shown on the right. High amplitude pressure waves are present corresponding in rate with the flutter waves of the simultaneous electrocardiogram.

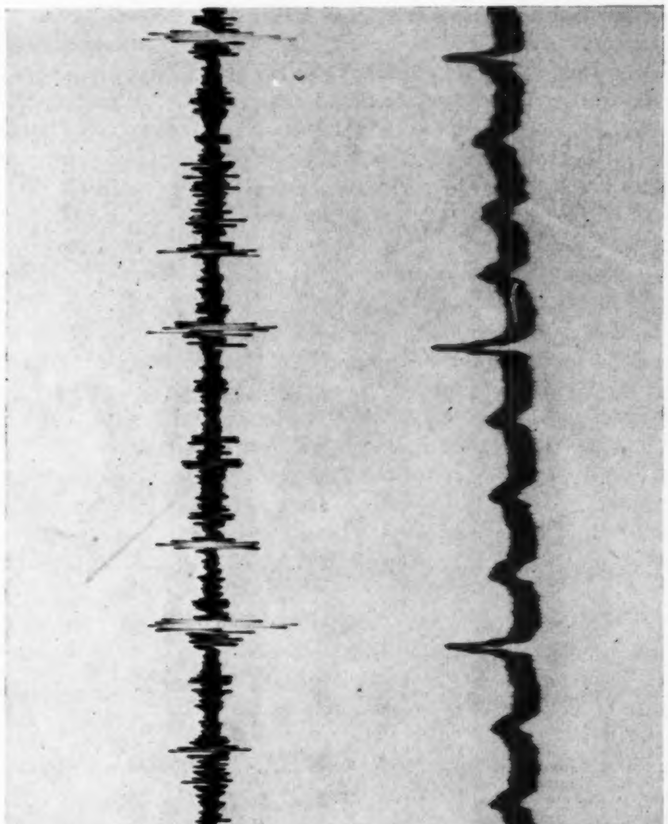


Fig. 2.—Case 1. A phonocardiogram recorded at the cardiac apex shows multiple accentuations in the intensity of the diastolic murmur indicated by X. These accentuations tend to correspond in frequency with that of the flutter waves of the simultaneous electrocardiogram.

34. Cournand, A.: Some Aspects of the Pulmonary Circulation in Normal Man and in Chronic Cardiopulmonary Diseases, Circulation **2**:641, 1950.
35. Miller, W. S.: The Lung, ed. 2, Springfield, Illinois, 1947, Charles C Thomas, Publisher.
36. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 6, Philadelphia, 1952, W. B. Saunders Company.
37. Ham, A. W.: Histology, ed. 2, Philadelphia, 1953, J. B. Lippincott Company.
38. Gall, E. A.: Personal communication.
39. Carlotti, J., Joly, F., Sicot, J. R., Voci, G., and Cazals, F.: Étude Physio-Pathologique de la Petite Circulation au Cours due Rétrécissement Mitral (Travail Basé sur 50 Cas), Arch. mal. coeur V **45**:412, 1952.
40. Mudd, J. G., Kistner, W. F., Hanlon, C. R.: The Course of Pulmonary Hypertension After Surgical Treatment of Mitral Stenosis, Official Program, Part II, Second World Congress of Cardiology, p. 140.
41. Carlotti, J., Soulie, P., Joly, F., Sicot, J. R., and Degeorges, M.: Postoperative Hemodynamic Studies Carried Out in 48 Cases of Mitral Stenosis, Official Program, Part II, Second World Congress of Cardiology, p. 109.
42. Fowler, N. O., Cubberly, R., and Dorney, E.: Pulmonary Blood Distribution and Oxygen Diffusion in Mitral Stenosis, Am. Heart J. **48**:1, 1954.
43. Halmágyi, D., Felkai, B., Iványi, J., Zsótér, T., Tényi, M., Szücs, Zs.: The Role of the Nervous System in the Maintenance of Pulmonary Arterial Hypertension in Heart Failure, Brit. Heart J. **15**:15, 1953.
44. Edwards, J. E., Tompkins, R. G., Hood, R. T., Jr., Kirklin, J. W., and Burchell, H. B.: Biopsy of the Lung and Cardiac Catheterization Studies in Patients Treated Surgically for Mitral Stenosis, J. Lab. & Clin. Med. **40**:795, 1952.
45. (a) Ankeney, J. L.: Interrelations of Pulmonary Arterial, "Capillary," and Left Atrial Pressures Under Experimental Conditions, Am. J. Physiol. **169**:40, 1952.
(b) Ankeney, J. L.: Further Experimental Evidence That Pulmonary Capillary Pressures do not Reflect Cyclic Changes in Left Atrial Pressure, Circulation Res. **1**:58, 1953.
46. (a) Connolly, D. C., Lev, R., Kirklin, J. W., and Wood, E. H.: Pulmonary Artery Wedge Pressures in Mitral Valve Diseases; Relationship to Left Atrial Pressure, Fed. Proc. **12**:28, 1953.
(b) Connolly, D. C., Tompkins, R. G., Lev, R., Kirklin, J. W., and Wood, E. H.: Pulmonary Artery Wedge Pressures in Mitral Valve Disease; Relationship to Left Atrial Pressure, Proc. Staff Meet., Mayo Clin. **28**:72, 1953.
(c) Connolly, D. C., Kirklin, J. W., and Wood, E. H.: The Relationship Between Pulmonary Artery Wedge Pressure and Left Atrial Pressure in Man, Circulation Res. **2**:434, 1954.
47. (a) Werkö, L., Varnauskas, E., Eliasch, H., Lagerlöf, H., Senning, A., and Thomasson, B.: Further Evidence That the Pulmonary Capillary Venous Pressure Pulse in Man Reflects Cyclic Pressure Changes in the Left Auricle, Circulation Res. **1**:337, 1953.
(b) Werkö, L., Varnauskas, E., Eliasch, H., and Thomasson, B.: The Influence of the Pulmonary Arterial Pressure on the Pulmonary Capillary Venous Pressure in Man, Circulation Res. **1**:340, 1953.
48. Björk, V. O., Malmström, G., and Uggla, L. C.: Left Atrial and Pulmonary "Capillary" Pressure Curves During Valsalva's Experiment, Am. Heart J. **47**:635, 1954.
49. Epps, R. G., and Adler, R. H.: Left Atrial and Pulmonary Capillary Venous Pressures in Mitral Stenosis, Brit. Heart J. **15**:298, 1953.

AURICULAR FLUTTER: A HEMODYNAMIC BASIS OF CLINICAL FEATURES

MALCOLM C. McCORD, M.D., AND S. GILBERT BLOUNT, JR., M.D.

DENVER, COLO.

CLINICIANS have been aware for many years of the occurrence of rapid neck vein pulsations in patients with auricular flutter.[1] Auscultatory phenomena peculiar to this cardiac arrhythmia have also been well described in the past.[2] These physical findings have been emphasized primarily as aids in the bedside detection of auricular flutter with little attention devoted to the value of these signs in appraising the underlying dynamic state of the cardiovascular system.

An investigation has been carried out in this laboratory regarding the basic hemodynamic characteristics of auricular contraction during flutter by an analysis of data obtained by right-heart catheterization in patients with this arrhythmia and with other types of auricular arrhythmias. An attempt has been made to determine the factors responsible for the development of the classical physical findings so that the clinical value of these signs may be extended.

Observations are presented on three representative patients with auricular flutter and on one patient with a supraventricular tachycardia.

MATERIAL AND METHODS

Right-heart catheterization was carried out in the usual manner. Pressures were determined using Statham strain gauges and a Hathaway recording apparatus. The zero point of reference was 10 cm. above the table with the patient supine. Auricular pressure tracings were obtained in six patients with auricular flutter, eleven patients with a supraventricular tachycardia, and in thirty-four patients with auricular fibrillation. Detailed presentation is given of three of the patients with auricular flutter as these patients exhibited varying clinical manifestation of the arrhythmia. One of the patients with a supraventricular tachycardia is presented for comparison.

CASE REPORTS

CASE 1.—H. K., a 21-year-old man had rheumatic fever at ten years of age and was noted to have valvular heart disease at that time. Progressively severe exertional dyspnea and ease

From the Cardiovascular Laboratory and Department of Medicine, The University of Colorado School of Medicine, Denver, Colo.

This study was supported by a United States Public Health Service Research Grant H-1208.

Received for publication April 13, 1955.

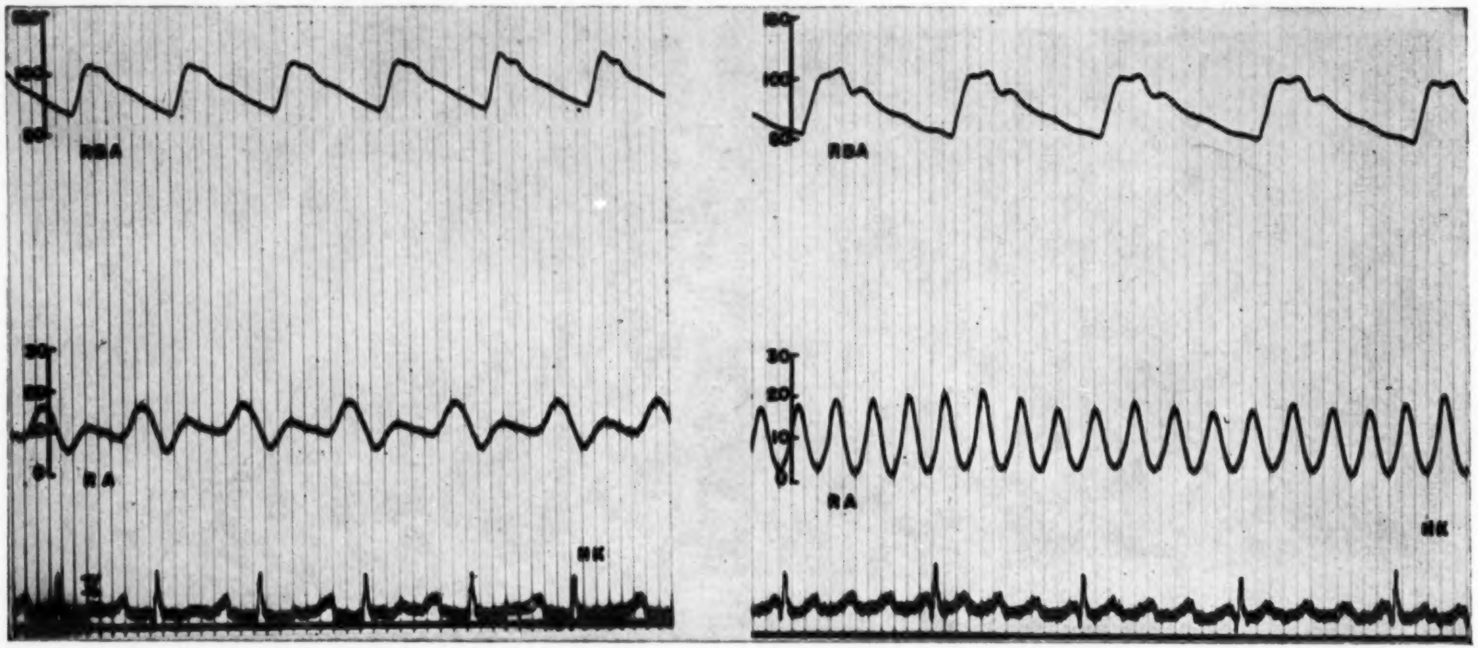


Fig. 1.—Case 1. The pressure tracing to the left demonstrates the right auricular pressure, *RA*, during sinus rhythm, showing high amplitude *a* waves. The right auricular pressure during auricular flutter is shown on the right. High amplitude pressure waves are present corresponding in rate with the flutter waves of the simultaneous electrocardiogram.

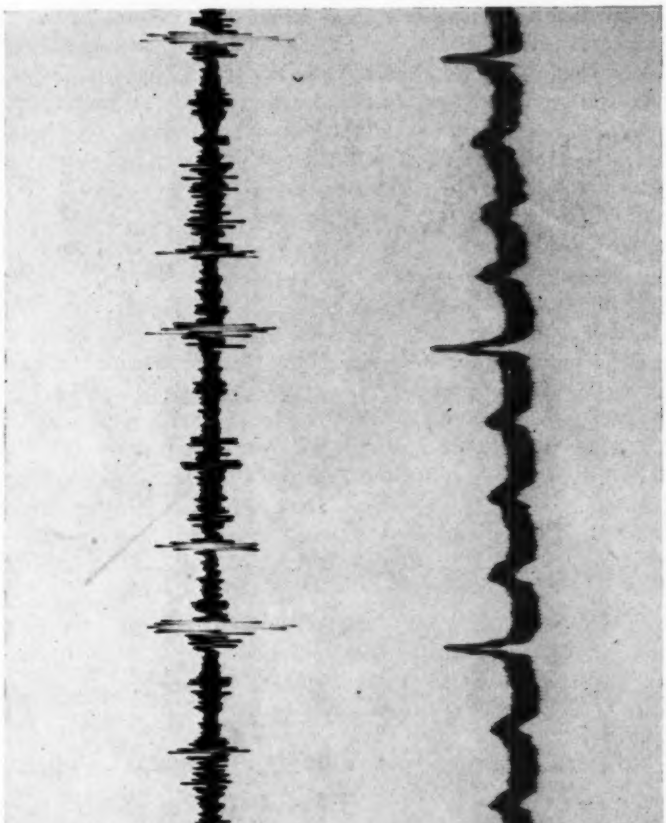


Fig. 2.—Case 1. A phonocardiogram recorded at the cardiac apex shows multiple accentuations in the intensity of the diastolic murmur indicated by *X*. These accentuations tend to correspond in frequency with that of the flutter waves of the simultaneous electrocardiogram.

of fatigue had occurred since the age of 15 years. Physical examination revealed a sinus rhythm with a rate of 88, a systemic blood pressure of 120/75 mm. Hg, extension of the hepatic margin 5 cm. below the right costal margin, and 1-plus pitting edema of the ankles. Auscultation revealed a harsh systolic murmur of Grade 2 intensity in the second right intercostal space and a high-pitched blowing diastolic murmur along the left sternal border. A rumbling diastolic murmur with presystolic accentuation was present in the fourth intercostal space to the left of the sternum and at the cardiac apex. The murmur in the tricuspid area increased in intensity during inspiration. The electrocardiogram demonstrated widening of the P-R interval to 0.28 sec. Peaked P waves 6 mm. in amplitude were present in precordial position V_2. Fluoroscopic examination revealed a normal vascular pattern in the lung fields. The superior vena cava was dilated and prominent. The over-all heart size was enlarged with a configuration suggesting enlargement of the right ventricle and of both auricles.

Cardiac catheterization demonstrated a pressure of 24/10 mm. Hg in the pulmonary artery, 28/0/3 mm. Hg in the right ventricle, and 17/5 mm. Hg in the right atrium. A pressure gradient of 10 mm. Hg was present from the right atrium to the right ventricle in early diastole. The cardiac index was 1.5 L./min./M.^{2} and the arteriovenous oxygen difference was 7.5 volumes per cent. The dominant pressure wave in the right auricular pressure tracing occurred in presystole with an onset 0.07 sec. following the onset of the P wave of the simultaneous electrocardiogram (Fig. 1). Auricular flutter occurred spontaneously at the conclusion of the study with the catheter tip at the right auricular level. Right auricular pressure waves were recorded averaging 18/4 mm. Hg in amplitude coincident in rate with the flutter waves of the electrocardiogram at 204 beats per minute (Fig. 1).

Physical examination revealed easily visible rapid pulsations in the cervical veins with the patient erect. Auscultation disclosed an alteration in the characteristics of the diastolic murmur in the tricuspid and mitral areas. In contrast to the single presystolic accentuation noted during a sinus rhythm, multiple accentuations in the intensity of the murmur were audible during diastole (Fig. 2).

Cardiac surgery was carried out by Dr. Henry Swan. Tight stenosis of the tricuspid and mitral valves was present and was ameliorated by digital valvuloplasty.

Case 2.—A. S., a 74-year-old woman was known to have valvular heart disease since the age of 49 years. Congestive heart failure first occurred at 69 years of age and had recurred intermittently since. Physical examination revealed an irregular radial pulse with a rate of 75. The systemic blood pressure was 160/82 mm. Hg, the hepatic margin was palpable 5 cm. below the right costal margin, and there was 2-plus pitting edema at the ankles. Examination of the neck veins revealed no pulsations with the patient erect. Faint rapid venous pulsations could be seen intermittently in the right supraclavicular fossa when the patient was supine. Auscultation revealed a Grade 1 rumbling apical diastolic murmur with no accentuation. The electrocardiogram demonstrated auricular flutter at a rate of 220 with a varying ventricular response. A left bundle branch block pattern was present. Fluoroscopic examination showed an over-all increase in heart size with a configuration indicating enlargement of the main pulmonary artery, the right and left auricles, and the right ventricle. Cardiac catheterization demonstrated an average pressure of 50/30 mm. Hg in the pulmonary artery, 50/2 mm. Hg in the right ventricle, and 7/4 mm. Hg in the right auricle. The cardiac index was 1.9 L./min./M.^{2}, and the arteriovenous oxygen difference was 6.7 volumes per cent. The right auricular pressure tracing showed pressure waves 2 to 4 mm. Hg in amplitude with a frequency corresponding to that of the flutter waves of the electrocardiogram (Fig. 3). The pulmonary arterial pressure tracing demonstrated low-amplitude pressure waves superimposed on the downstroke of the pulmonary pressure wave corresponding in frequency with the auricular flutter rate (Fig. 3).

Case 3.—R. M., a 79-year-old woman, had noted progressively severe dyspnea for two years. Dependent edema and orthopnea had occurred two months prior to admission. Physical examination revealed no pulsations in the neck veins. The systemic blood pressure was 240/125 mm. Hg, the pulse was regular with a rate of 45, the inferior hepatic margin was palpable 2 cm. below the right costal margin, and there was 2-plus pitting edema at the ankles. Auscultation revealed a faint high-pitched blowing diastolic murmur along the left sternal border and a Grade 2

apical systolic murmur. Rapid clicking sounds were audible during diastole in the second and third intercostal spaces, 4 cm. to the left of the sternal border. The electrocardiogram demonstrated auricular flutter with a rate of 340. Complete atrioventricular block was present with an idioventricular rhythm at a rate of 45.

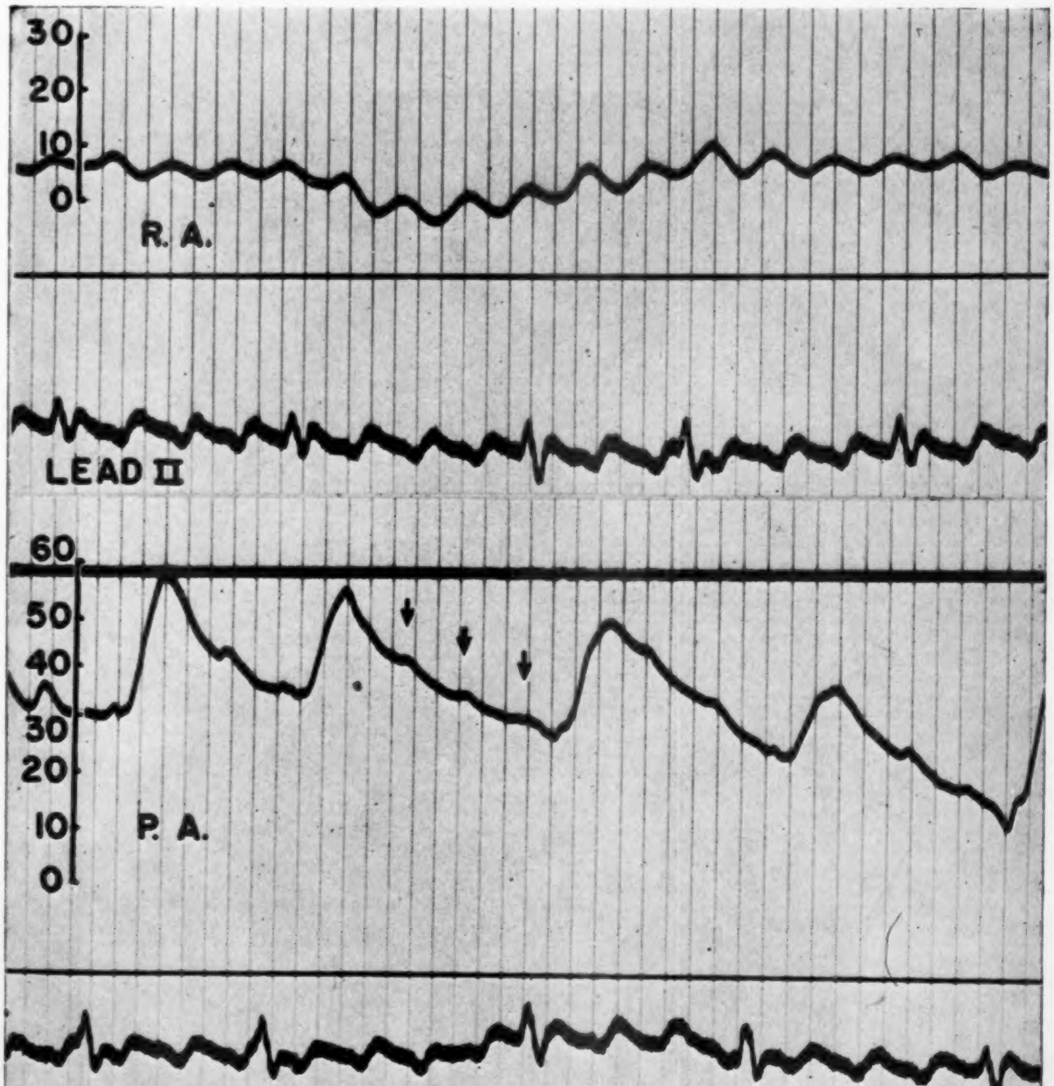


Fig. 3.—Case 2. *R.A.*, right auricle; *P.A.*, pulmonary artery. The right auricular tracing shows a slow-frequency pressure variation related to respiration with low-amplitude rapid waves coincident with the flutter waves of the electrocardiogram. Small pressure elevations are noted superimposed on the pulmonary arterial pulse wave (arrows) again corresponding to the frequency of the flutter waves of the electrocardiogram.

Fluoroscopic examination revealed right pleural effusion, an increase in over-all heart size, and a ventricular configuration suggesting left ventricular hypertrophy. Catheterization of the right auricle revealed an average pressure at this level of 6/0 mm. Hg. Analysis of the pressure

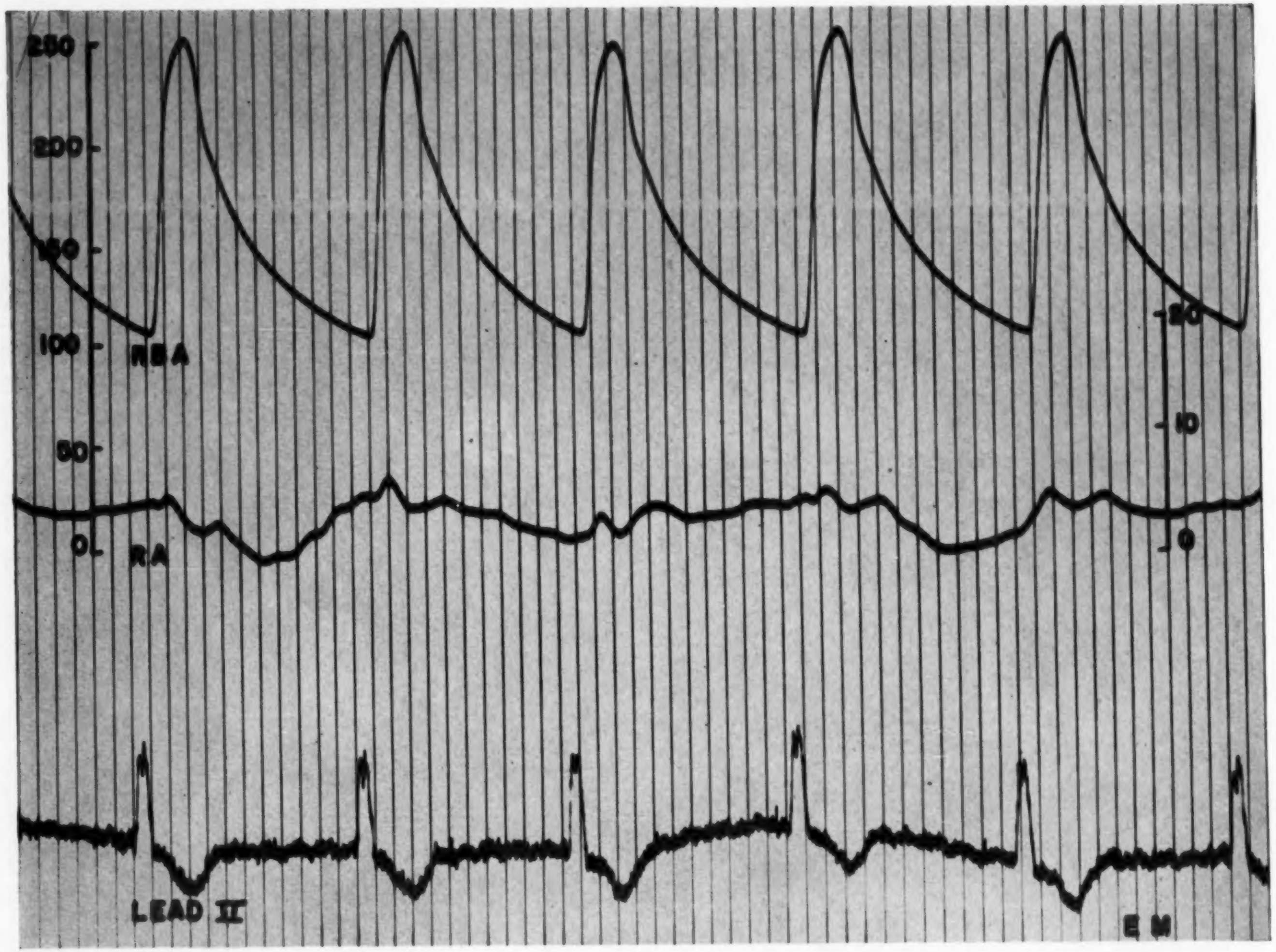


Fig. 4.—Case 3. The right brachial arterial tracing, *RBA*, indicates arterial hypertension. The right auricular pressure shows respiratory variation and shows a *c* and *v* wave related to each ventricular systole. No consistent pressure waves are discernible corresponding to the flutter waves of the electrocardiogram.

tracing revealed pressure fluctuations occurring only in relation to ventricular contraction. Accentuated *c* and *v* waves occurred suggesting mild tricuspid insufficiency. No pressure phenomena were discernible related to auricular activity (Fig. 4).

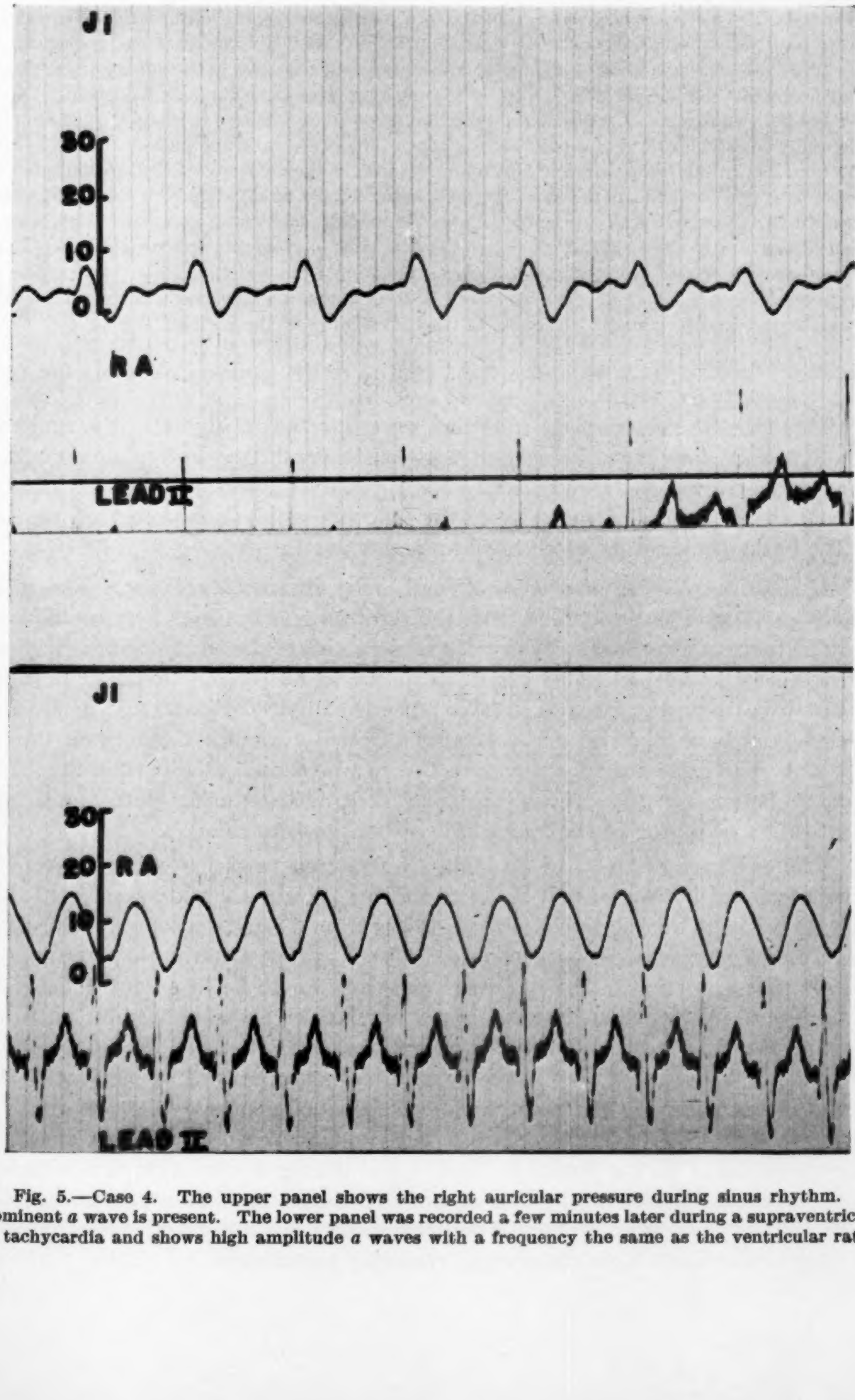


Fig. 5.—Case 4. The upper panel shows the right auricular pressure during sinus rhythm. A prominent *a* wave is present. The lower panel was recorded a few minutes later during a supraventricular tachycardia and shows high amplitude *a* waves with a frequency the same as the ventricular rate.

Case 4.—J. I., an 11-year-old boy, one of twins, had been retarded in growth and had a diminished exercise tolerance since infancy. A murmur had been heard since early childhood. Physical examination revealed cardiac enlargement and a systolic thrill in the left fourth intercostal space. Auscultation disclosed a harsh, systolic murmur of Grade 5 intensity in the left fourth intercostal space and a short mid-diastolic murmur at the apex. No neck vein pulsations were noted. The electrocardiogram demonstrated a pattern suggesting left and right ventricular hypertrophy. Fluoroscopic examination demonstrated a considerable increase in the vascularity of the lung fields with enlargement and increased amplitude of pulsation in the pulmonary arteries. The over-all heart size was increased with a configuration suggesting enlargement of the right auricle and of both ventricles. Cardiac catheterization revealed an increase in blood oxygen content at the right ventricular level of 3 volumes per cent. The pressure in the pulmonary artery was 56/46 mm. Hg, in the right ventricle 56/2 mm. Hg, and in the right auricle 8/0 mm. Hg. The pressure tracing recorded from the right auricle demonstrated a moderately high *a* wave resulting from right auricular contraction (Fig. 5). A supraventricular tachycardia occurred at the termination of the study. The right auricular pressure tracing during this arrhythmia revealed an increased amplitude of the right pressure wave resulting from right auricular contraction to average levels of 16/4 mm. Hg. The frequency of these augmented *a* waves was the same as the ventricular rate and presumably the same as the contractions of the auricles.

DISCUSSION

The patients presented at this time were selected to illustrate the range of hemodynamic phenomena associated with auricular flutter and to demonstrate the variable clinical patterns reflecting these dynamic activities. On the basis of the findings in these illustrative cases the following analysis is presented regarding the basic mechanisms involved in auricular flutter.

Mechanism of Impulse Formation During Auricular Flutter.—The well-defined pressure waves recorded from the right auricle in Cases 1 and 2 indicate the occurrence of a mechanically effective contraction of the auricular myocardium during auricular flutter. This aspect of auricular flutter has been documented for many years on the basis of jugular pulse tracings.[1,3] Roentgenkymographic observations have likewise demonstrated discrete auricular movements during flutter.[4,5] The right auricular pressure tracings presented at this time thus confirm the occurrence of effective auricular contraction during flutter and add quantitative definition of the magnitude of the pressure changes.

This evidence of effective auricular contraction tends to substantiate the views advanced by Scherf and Schott,[6] and by Prinzmetal and associates,[7] that activation of the auricle during flutter arises from a single ectopic focus rather than from a continuous circus mechanism. A circus type of activation presumably would cause a portion of the auricular myocardium to be in a contracted state at all times. Under such circumstances a relatively static auricular chamber pressure would be expected to occur, resembling that recorded during auricular fibrillation. It is difficult to conceive of a circular pathway of activation resulting in auricular contractions capable of producing pulse waves 12 mm. Hg in amplitude as demonstrated in Case 1. The similarity of the right auricular pressure patterns during flutter in Case 1 and during a supraventricular tachycardia in Case 4 is striking. This common pressure pattern suggests that the mechanism of activation in these two arrhythmias is similar and differs only in the rate of discharge from the ectopic auricular pacemaker.

Factors Determining the Magnitude of Pressure Waves Resulting From Auricular Contraction During Flutter.—The findings in the cases presented indicate that the amplitude of the auricular pressure waves seen in auricular flutter is directly related to the degree of hypertrophy of the auricular myocardium. A severe obstruction to right auricular outflow was present in Case 1 in the form of tricuspid valve stenosis. An increased residual blood volume thus accumulated in the right auricle with consequent dilatation and hypertrophy of the right auricular myocardium. This hypertrophied right auricular musculature produced an increased tension during contraction which was manifested by a high-amplitude *a* wave during sinus rhythm and a strikingly high-amplitude pressure wave during auricular flutter. A moderate stimulus to right auricular hypertrophy was afforded in Case 2 by the existence of right ventricular systolic hypertension with right ventricular hypertrophy. This mechanism resulting in right auricular hypertrophy has been detailed in a previous publication from this laboratory.[8] The high-amplitude right auricular pressure waves in Case 4 can be ascribed to this same mechanism. No stimulus for hypertrophy of the right auricle was present in Case 3, where the basic lesion was systemic arterial hypertension. Consequently no increase in the tension of right auricular contraction occurred, and no pressure waves could be detected within the right auricle at catheterization. This pattern was similar to that recorded during auricular fibrillation where pressure changes related to auricular contraction were seldom detectable.

The magnitude of auricular pressure waves resulting from auricular flutter therefore is governed by the same factors that control the magnitude of auricular pressure waves during sinus rhythm. The pressure waves produced by a fluttering auricle may therefore be considered as rapid *a* waves.

Factors Determining the Presence of Neck Vein Pulsations During Auricular Flutter.—The presence of rapid neck vein pulsations detectable at the bedside in patients with auricular flutter depends primarily upon the magnitude of the pressure waves generated by the fluttering right auricle. Secondary considerations include such factors as obesity obscuring the neck veins and the effort made to position the patient in such a manner to facilitate observation of the pulsations. Observation of the cervical veins at successive degrees of elevation between supine and erect is particularly important in patients with congestive failure. In the presence of an elevated mean venous pressure level the cervical veins may be completely distended and show no pulsations when the patient is supine. It is apparent, from the patients described at this time, that high-amplitude pressure waves are necessary to produce clearly defined clinical findings. The faint pulsations described in Case 2 would not have been observed unless a particular effort to elicit this sign had been made. The presence of rapid pulse waves in the neck veins of patients with auricular flutter thus not only indicates the type of cardiac rhythm but indicates further that the right auricle is significantly hypertrophied. These waves carry the same clinical significance as prominent presystolic waves or "giant" *a* waves during sinus rhythm. Other clinical signs may then be integrated to determine the cause of

the auricular hypertrophy such as pulmonary hypertension, pulmonic stenosis, or tricuspid stenosis.

Auscultatory Phenomena Associated With Auricular Flutter.—The alteration in the characteristics of the diastolic murmur in Case 1 with the onset of auricular flutter constitutes an unusual auscultatory manifestation of this arrhythmia. The appearance of a diastolic murmur following the onset of auricular flutter has been described by Luisada.[4] The phenomenon of multiple accentuations of a diastolic murmur described at this time is interpreted as indicating a hypertrophied auricle producing a high-velocity flow through the narrowed atrioventricular valves with each auricular contraction.

The rapid clicking sounds described in Case 3 represent a more common form of auscultatory finding in auricular flutter. These sounds were first recorded by Bennet and Kerr in 1931[2] and have subsequently been analyzed in greater detail.[9-11] The sound tracing presented by Biehl and Simon illustrates these sounds very clearly.[11] No conclusive explanation for the origin of these clicking heart sounds has been established. It is probable, however, they arise as a result of contact between the auricle and a contiguous mediastinal structure such as the pleura. Hypertrophy of the auricle with an elevated right auricular pressure is apparently not a necessary factor in the production of these sounds, since they were audible in Case 3 where no auricular pressure waves were recorded. The occurrence of such clicking sounds is therefore considered as a fortuitous event, accentuated by the long diastole afforded by complete heart block, and possibly facilitated by serosal reaction such as may occur with pleural effusion.

Transmission of Auricular Pressure Waves to the Arterial Systems.—Auricular pressure waves were demonstrated superimposed on radial arterial pulse tracings during complete heart block by Lewis[3] and by Mackenzie.[12] Mackenzie also published cardiac apex tracings demonstrating flutter waves during diastole.[1] Howarth has recently presented direct brachial arterial pressure tracings demonstrating pressure waves of auricular origin during auricular flutter and other auricular arrhythmias.[13] Harvey and associates have described the presence of auricular flutter waves superimposed on pulmonary arterial and right ventricular pressure tracings.[14] The auricular pressure waves superimposed on the pulmonary arterial pressure wave in Case 2 (Fig. 3) demonstrate this interesting hemodynamic phenomenon. The mechanism responsible for the transmission of auricular pressure phenomenon to the arterial systems is not established. Lewis suggested that these auricular pressure waves noted on arterial pulse tracings resulted from mechanical contact between the auricles and the aorta.[3] However, the view that these low-amplitude pressure waves reflect movements of the semilunar valves is considered more likely. During diastole the auricular pressure changes are transmitted directly to the ventricular cavity and could readily cause minor movements in the semilunar valve leaflets.

CONCLUSIONS

Observations in three patients with auricular flutter are presented to illustrate the varying clinical and hemodynamic manifestations of this arrhythmia.

Mechanically effective auricular contraction during flutter is established by the demonstration of discrete right auricular pressure waves. The similarity of the right auricular pressure curves during auricular flutter and during supraventricular tachycardia is demonstrated. The magnitude of the auricular pressure waves is shown to be related to the degree of hypertrophy of the right auricle. Auscultatory phenomena peculiar to auricular flutter are described and the origins discussed.

SUMMARIO IN INTERLINGUA

Es presentate observationes clinic e hemodynamic super tres patientes con flutter auricular e un patiente con tachycardia supraventricular. Esseva registrate undas del pulso auricular que correspondeva al contraction auricular de simultanee electrocardiogrammas in omne casos con un exception. In duo patientes rapide pulsationes del venas cervical esseva presente; e in un altere, un rapide clic del corde. In un patiente un alteration in le qualitate de un murmure diastolic occurreva al inception de flutter auricular. Nos presenta le hypothese que le amplitude del unda del pression dexteroauricular durante flutter auricular, assi como le accompaniante constatationes clinic, reflecte le grado de hypertrophia del auricula dextere.

REFERENCES

1. Mackenzie, J.: Diseases of the Heart, ed. 4, London, 1925, Oxford University Press.
2. Bennet, D. W., and Kerr, W. J.: A Note on Auricular Sounds in a Case of Auricular Flutter, Heart **16**:109, 1931.
3. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, 1925, Shaw & Sons, Ltd.
4. Luisada, A.: The Heart Beat; Graphic Methods in the Study of the Cardiac Patient, New York, 1952, Paul B. Hoeber, Inc.
5. Lewis, J. L., and Terry, L. L.: Electrokymography—An Appraisal of Its Present Clinical Status, Ann. Int. Med. **32**:36, 1950.
6. Scherf, D., and Schott, A.: Extrasystoles and Allied Arrhythmias, New York, 1953, Grune and Stratton, Inc.
7. Prinzmetal, J., Corday, E., Brill, I. C., Oblath, R. W., and Kruger, H. E.: The Auricular Arrhythmias, Springfield, Ill., 1952, Charles C Thomas, Publisher.
8. McCord, M. C., Komesu, S., and Blount, S. G., Jr.: The Characteristics of the Right Atrial Pressure Wave Associated With Right Ventricular Hypertrophy, AM. HEART J. **45**:706, 1953.
9. Hecht, H. H., and Myers, G. B.: Auricular Heart Sounds in Auricular Flutter, AM. HEART J. **29**:610, 1945.
10. Rattigan, J. P., Byrnes, W. W., Kraus, H., and Sise, H. S.: Audible Auricular Heart Sounds in Auricular Flutter, New England J. Med. **246**:130, 1952.
11. Biehl, J. P., and Simon, D. L.: Auricular Sounds in a case of Auricular Flutter, Am. J. Med. **15**:134, 1953.
12. Mackenzie, James: New Methods of Studying Affections of the Heart, Brit. Med. J. **1**:519, 1905.
13. Howarth, S.: Atrial Waves on Arterial Pressure Records in Normal Rhythm, Heart Block, and Auricular Flutter, Brit. Heart J. **16**:171, 1954.
14. Harvey, R. M., Cournand, A., and Ferrer, M. I.: Cardiocirculatory Performance in Atrial Flutter, Program of the 46th Annual Meeting of the American Society for Clinical Investigation, p. 31, 1954.

SIMULTANEOUS LEFT AND RIGHT ATRIAL PRESSURE CURVES DURING VALSALVA'S EXPERIMENT

VIKING OLOV BJÖRK, M.D., AND GUNNAR MALMSTRÖM, M.D.

STOCKHOLM, SWEDEN

SIMULTANEOUS pressure recordings from the left (LA) and the right atrium (RA) have been performed in man with intact thorax. In this communication we want to present the findings from the simultaneous pressure measurements in the two auricles during and after periods of increased intrathoracic pressure, i.e., Valsalva's experiments in cases with and without mitral stenosis.

METHOD

The left atrial pressure was recorded by direct right-sided paravertebral puncture of the left auricle according to Björk.[1,3] The right auricular pressure was recorded through a catheter introduced in the usual way for heart catheterization. The pressure measurements were carried out with a strain-gauge receptor type Swema EMT 456, using Elema six-lead channel electrocardiograph as the optical recording device. The pressures were obtained by planimetric integration of the area between the pressure curves and the calibration zero line.

The patient was asked to take a deep inspiration immediately followed by a forceful expiration through a bottle of mercury.

RESULTS

1. The intrathoracic pressure rise immediately caused a simultaneous elevation of the pressures in the left and right auricles.

2. The increase of pressure, i.e., the difference between the mean pressure in the beginning of the Valsalva plateau and the mean pressure before this maneuver was of the same order in the left and right auricle only in Case 8, having a normal resting left atrial pressure and normal mitral valves. In all the other cases (1 to 7) with mitral stenosis and a considerably elevated resting left atrial pressure, the pressure increase was much higher in the right atrium (32 mm. Hg) than in the left atrium (21 mm. Hg).

From Sabbatsberg Hospital, Stockholm, Sweden; Surgeon-in-Chief: C. Crafoord, M.D., Professor.

Received for publication April 22, 1955.

TABLE I. SIMULTANEOUS RIGHT AND LEFT ATRIAL PRESSURE* MEASUREMENTS DURING VALSALVA'S EXPERIMENT

		PRESSURE INCREASE IN MM. HG	
		RIGHT ATRIUM	LEFT ATRIUM
Experiment Mitral stenosis	1	33	23
	2	34	27
	4	31	20
	6	22	14
	7	39	20
Mean value		32	21
Experiment	8	28	27

*The increase of pressure, i.e., the difference between the pressure in the beginning of a Valsalva experiment and the pressure before this maneuver in five cases of mitral stenosis, 1 to 7, and one case of pericarditis, 8. Pressures are given in mm. Hg. In Cases 1 to 7 the resting left atrial pressure was considerably elevated; in Case 8 on the other hand the left atrial pressure was normal.

3. During the Valsalva maneuver there was a significant decrease of pressure in the left auricle (mean pressure = −5.6 mm. Hg; see Table II). At the same time only a slight decrease (mean pressure = −1 mm. Hg) or even an increase of pressure in some cases was observed in the right auricle. The pressure increases in the beginning and at the end of some Valsalva experiments in the simultaneously obtained left and right auricular pressure curves are given in Table II.

4. The sudden release of the intrathoracic pressure was immediately followed by a simultaneous drop in the right and left auricle to subnormal values especially low in the left atrium. Then followed a poststraining pressure overshoot in the left atrium in cases with mitral stenosis. No pressure overshoot was observed in the left atrium in Case 8 with normal mitral valves, see Table III.

TABLE II. THE DIFFERENCE BETWEEN THE SIMULTANEOUSLY OBTAINED PRESSURES IN THE RIGHT AND LEFT ATRIUM, IN THE BEGINNING AND AT THE END OF A VALSALVA'S EXPERIMENT*

EXPERIMENT	RIGHT ATRIUM	LEFT ATRIUM
1	51 − 50 = +1	39 − 46 = −7
2	46 − 48 = −2	37 − 44 = −7
3	29 − 36 = −7	51 − 58 = −7
4	47 − 47 = 0	38 − 39 = −1
5	59 − 56 = +3	61 − 68 = −7
6	20 − 15 = +5	29 − 32 = −3
7	23 − 33 = −10	27 − 38 = −11
8	28 − 27 = +1	25 − 23 = −2
Mean difference	−1 mm. Hg	−5.6 mm. Hg

*Experiments 1 to 7 were performed on cases with mitral stenosis and a considerably elevated resting left atrial pressure. In experiment 8 the resting left atrial pressure was normal.

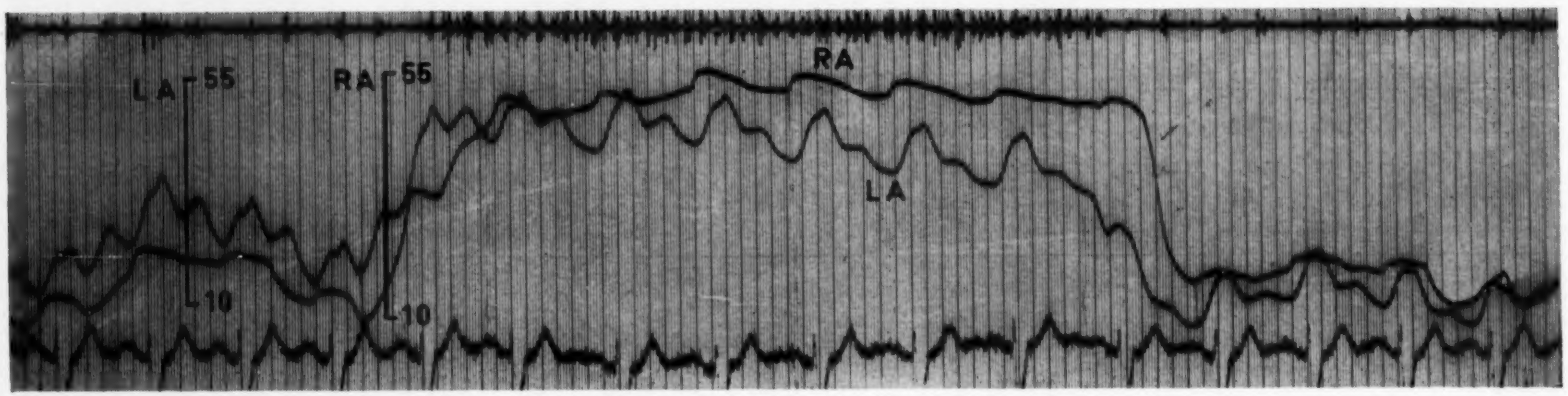


Fig. 1.—Experiment 1. Simultaneously obtained pressure curves from the left atrium (*LA*) and right atrium (*RA*) during Valsalva's experiment in a case of mitral stenosis. There is a gradual decrease of pressure in the left atrium at the same time as the right atrial pressure is remaining at a constant level, compare Table II.

TABLE III. SIMULTANEOUSLY OBTAINED PRESSURES IN THE LEFT AND RIGHT ATRIUM DURING THE POSTSTRAINING PERIOD*

EXPERIMENT	IMMEDIATELY		LATER	
	RIGHT ATRIUM	LEFT ATRIUM	RIGHT ATRIUM	LEFT ATRIUM
1	17	12		
3	8	26		
6	0	13	0	27
7	1	9	2	26
8			2	3

*Cases 1 to 7 have mitral stenosis; in Case 8 the mitral valves were normal. The pressure was measured immediately after Valsalva's experiment, from 1 to 3 seconds after the release of pressure; and later from 5 to 7 seconds after the release of pressure.

DISCUSSION

In experimental animals it has been shown that the right atrial system is more distensible than the left.

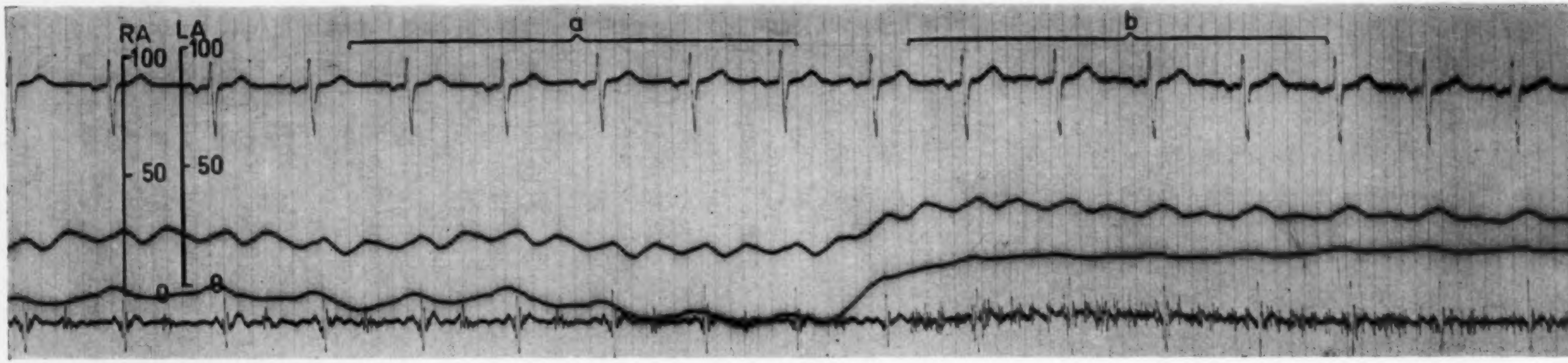
In cases of mitral stenosis the resting pressure in the left atrium considerably exceeds the right atrial pressure. The left atrial wall becomes thicker than the right. The pressure increase in the right atrium was found much higher than in the left atrium during Valsalva's experiment with simultaneous pressure measurements in the left and right atrium in cases of mitral stenosis. No such difference in pressure increase was found in a case with normal mitral valves and normal resting left atrial pressure. We therefore believe the more pronounced pressure increase in the right auricle compared to the pressure in the left auricle in cases of mitral stenosis during Valsalva's experiment may be due to the thin wall of the right atrium as compared to the left.

During Valsalva's experiment we have previously found a gradual pressure fall in the left atrium. This is ascribed to a damming up of blood in the venous system with a diminished flow of blood through the lungs.

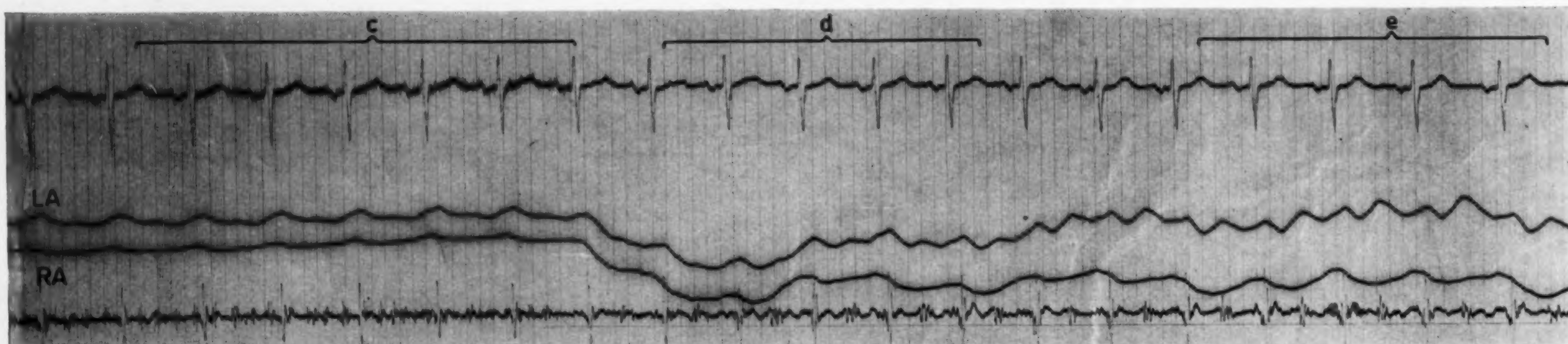
In the right atrium, however, the pressure during Valsalva's experiment remains on a more constant level or may even be increased. The right atrial system is in a direct connection with the venous system where blood is accumulating under a gradually increasing pressure. This may explain the difference in pressure in the two atria at the end of a Valsalva experiment.

In the poststraining period there is a pressure rise in the right atrium due to the inability of the pulmonary vascular bed with increased resistance to permit the passage of extra accumulated blood. This pressure overshoot in the right atrium will be less in cases with a normal pulmonary resistance. In these cases a comparatively larger pressure overshoot will be found in the left atrium in front of the mitral stenosis. No pressure overshoot was found in either atrium in a case with normal mitral valves.

We have not performed a larger series of Valsalva's experiment during left-heart catheterization, as an air embolism with cerebral symptoms occurred in one case. After two days all symptoms had disappeared, but after that accident we do not consider it justifiable to perform this procedure.

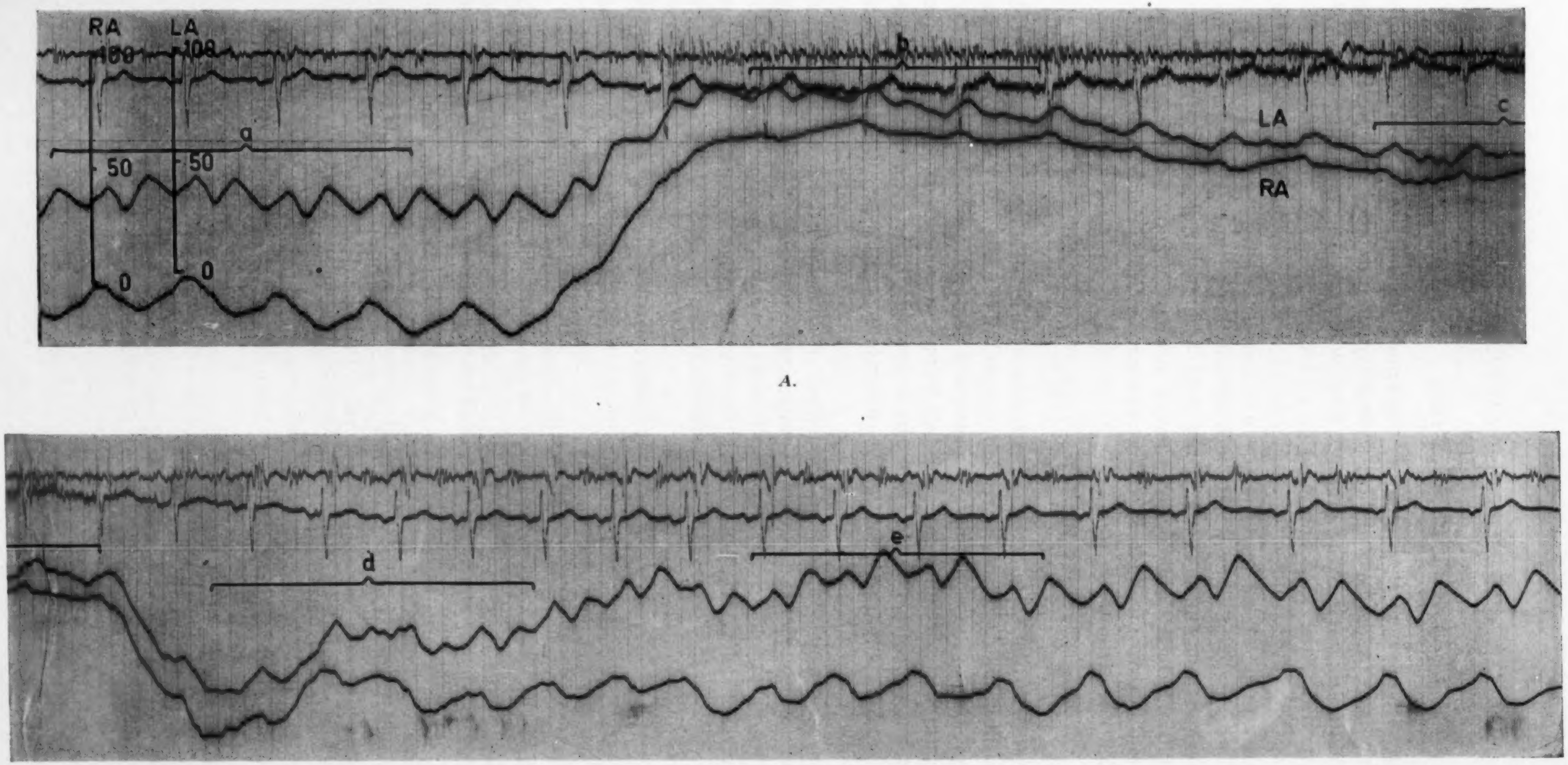


A.



B.

Fig. 2.—Experiment 6. *A* and *B*. *B* is a continuation of *A*. Valsalva's experiment in a case of mitral stenosis results in a more pronounced pressure increase in the right atrium than in the left atrium, compare Table I. The poststraining pressure overshoot, on the other hand, is more pronounced in the left atrium in front of the stenosed mitral valve. *a* = Before, *b* = Beginning, *c* = End, *d* = Immediately, *e* = Later after the Valsalva experiment.



A.

B.

Fig. 3.—Experiment 7. *A* and *B*. *B* is a continuation of *A*. In a more forceful Valsalva's experiment in a case of mitral stenosis the same relation in pressures in the right and left atrium are found during and after the straining period as in experiment 6, see Fig. 2.

SUMMARY

When a Valsalva experiment is performed during simultaneous pressure measurements in the left and right atrium a typical difference in the two curves will be found. The left atrial pressure level will slowly decrease during a Valsalva experiment due to a damming up of blood in the venous system. The pressure in the right atrium on the other hand will not decrease as much during the Valsalva's experiment, or it may even increase.

The pressure in a thick-walled left atrium due to mitral stenosis will not increase as much as the pressure in the right atrium during a Valsalva experiment. In the poststraining period there is a more pronounced pressure overshoot in the left atrium in front of mitral stenosis than in the right atrium or in a normal left atrium.

SUMMARIO IN INTERLINGUA

Si le mesuration simultanee del pressiones in le atrios sinistre e dextere es executate sub le conditiones del experimento de Valsalva, le duo resultante curvas exhibi typic differentias. Le nivello pressional del atrio sinistre se abassa lentemente durante le experimento de Valsalva a causa del accumulation de sanguine in le systema venose. Del altere latere, le pression in le atrio dextere non se reduce a grados comparabile. Illo pote mesmo augmentar se durante le experimento.

In un atrio sinistre a pariete spissificate in consequentia de stenosis mitral le pression sub conditiones de Valsalva non accresce tanto como in le atrio dextere. Durante le relaxation post le experimento de Valsalva il ha un plus extreme hypercorrection del pression in le atrio sinistre de patientes con stenosis mitral que in le atrio dextere o que in le atrio sinistre normal.

REFERENCES

1. Björk, V. O., Malmström, G., and Uggla, L. G.: Left Auricular Pressure Measurements in Man, Ann. Surg. **138**:718, 1953.
2. Björk, V. O., Malmström, G., and Uggla, L. G.: Left Atrial and Pulmonary "Capillary" Pressure Curves During Valsalva's Experiment, Am. Heart J. **47**:635, 1954.
3. Björk, V. O.: Direct Pressure Measurement in the Left Atrium, the Left Ventricle and the Aorta, Acta Chir. Scandinav. **107**:466, 1954.
4. Elisberg, E., Singian, E., Miller, G., and Katz, L. N.: The Effect of the Valsalva Maneuver on the Circulation, III. The Influence of Heart Disease on the Expected Poststraining Overshoot, Circulation **7**:880, 1953.
5. Little, R. C.: Volume Elastic Properties of the Right and Left Atrium, Am. J. Physiol. **158**:237, 1949.
6. Opdyke, D. F., Duomarco, J., Dillon, W. H., Schreiber, H., Little, R. C., and Seely, R. D.: Study of Simultaneous Right and Left Atrial Pressure Pulses Under Normal and Experimentally Altered Conditions, Am. J. Physiol. **154**:258, 1948.
7. Rushmer, R. F.: Circulatory Effects of Three Modifications of the Valsalva Experiment, Am. Heart J. **34**:399, 1947.

AN EXTERNAL CARDIAC PACEMAKER IN THE TREATMENT OF STOKES-ADAMS SYNDROME: REPORT OF THREE CASES

ISADORE ROSENFELD, M.D.,* AND HAROLD N. SEGALL, M.D.

MONTREAL, CANADA

THE doctor at the bedside of a patient exhibiting attacks of Stokes-Adams syndrome has experienced a sense of inadequacy and frustration—all the more so in this era of "miracle drugs" and modern electronics. For almost 100 years, the possibility of reactivating an arrested heart by means of electrical stimulation has intrigued a succession of investigators in all parts of the world. The result has been an array of techniques most of which have proved to be ineffectual.

In 1862, Walshe[1] discussed the possibility of causing the heart to contract by the use of faradic stimulation of the sympathetic nerve trunks. This was followed by actual attempts of European workers to reanimate the arrested heart by passing electric currents through the chest wall, but without success. Since then, various devices were developed, notably by Hyman, all of which caused cardiac contraction. These instruments operated on the principle of direct stimulation of the myocardium by different types of needles, electrodes, or needle electrodes. In 1932, Hyman[2] reported the development of such a special needle electrode which could carry a stimulating current to the heart muscle. He inserted this into the right auricular wall of animals and was able to stimulate the heart to contract. In 1951, Callaghan and Bigelow[3] described the satisfactory control of heart action by an electrical artificial pacemaker. Their best results were obtained by placing the stimulating electrode in the superior vena cava against the deep surface of the sinoauricular node. The clinical and practical limitations of this apparatus were self-evident. In 1952, Zoll[4] described the successful stimulation of the heart in two patients with complete heart block and ventricular standstill. The apparatus consisted of subcutaneous needle electrodes attached to a thyratron physiologic stimulator generating periodic impulses of direct current. In a more recent report, Zoll and associates[5] describe this apparatus as further modified so that electrodes placed on the skin surface of the chest wall may be used. It is a modification of existing physiologic stimulators producing a monophasic rounded electric impulse of two or three milliseconds duration. The two controls on the apparatus permit variation in frequency of impulse formation from 30 to 180 per minute, and the amplitude varies from zero to 150 volts. We used this instrument† in three cases reported here.

From the Department of Cardiology, Jewish General Hospital, Montreal, Canada.
Received for publication April 19, 1955.

*Mona Bronfman Sheckman, Research Fellow in Cardiology.

†Manufactured by the Electrodyne Company, Norwood, Mass.

CASE REPORTS

CASE 1.—J.A., an 82-year-old white male, was admitted to the Jewish General Hospital the evening of Oct. 5, 1954. Except for the fact that he was a mild diabetic controlled on diet alone, and hypertensive, with arterial pressures of 220/120 mm. Hg, he had been in satisfactory health until the day prior to admission. He returned home from work, rested, and then went to bed. He awoke at 4:15 A.M. complaining of "indigestion," and a few minutes later developed a Stokes-Adams attack which lasted about two minutes. The next day, these attacks recurred at the rate of three an hour. At noon, there was sudden onset of severe substernal pain, continuous in nature. This pain did not radiate. No further details about the pain could be obtained. He was admitted about 5 P.M.

Physical examination at the time of admission revealed an elderly, well-preserved white male in considerable respiratory distress, undergoing frequent Stokes-Adams attacks. The arterial pressure was 140/0 mm. Hg. The radial pulse was regular at a rate of 20 per minute. The chest was emphysematous, and the breath sounds distant A few rhonchi were heard on deep inspiration. Heart sounds were barely audible. The patient responded to deep pain sensation, and occasionally to persistent loud vocal stimuli. Deep reflexes were not obtainable, and there was bilateral plantar extension. Corneal reflexes were present. Respirations were Cheyne-Stokes in character. Rectal temperature was 100° F. A catheter specimen of urine revealed a four-plus test for sugar, but no acetone or diacetic acid. The blood sugar at this time was 149 mg. per cent and the carbon dioxide combining power 45 volumes per cent. An electrocardiogram revealed complete heart block with a ventricular rate of 20 per minute.

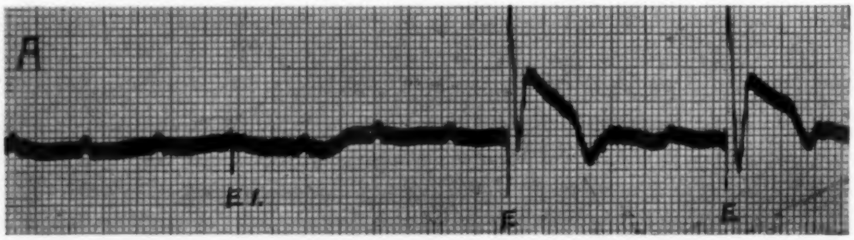


Fig. 1.—Case 1. Lead aV$_F$. Ventricular asystole interrupted by electrical stimuli (*E*) from pacemaker. Note stimulus E1 too weak to produce ventricular contraction.

The patient was given oxygen, Adrenalin, 1 c.c. of a 1/1000 solution subcutaneously, and ephedrine 30 mg. intramuscularly. Within two hours after admission, the pulse increased in rate to 52 per minute, with a corresponding arterial pressure of 170/58 mm. Hg. The electrocardiogram revealed sinus rhythm with right bundle branch block, but no evidence of recent infarction. With the increase in pulse from 20 to 52 beats per minute, there was some clearing of the sensorium. For another four hours after admission the pulse continued at low normal levels, reaching a maximum of 64 per minute with the arterial pressure 245/98 mm. Hg. Shortly thereafter, however, bradycardia recurred, with a pulse rate of 32 per minute and arterial pressure of 140/50 mm. Hg. A three-minute clonic convulsion was noted at 12:45 A.M., and during the next hour there were periods of complete ventricular asystole lasting from 15 to 45 seconds. Each asystolic period was accompanied by a typical Stokes-Adams convulsive attack.

At 1:45 A.M., the cardiac pacemaker was applied. During the first two hours the apparatus was used only to ward off threatened Stokes-Adams attacks. This it did on each occasion. The apparatus was initially set at a rate of 60 impulses per minute. It was found that a voltage large enough to convey each impulse through to the myocardium, and hence cause a radial pulse synchronous with the impulses of the apparatus, was very painful. No sedation had yet been given because of the already depressed higher centers. Each electrical impulse associated with an amplitude of 50 volts or higher caused ventricular contraction which was accompanied by simultaneous contraction of the muscles of the chest, particularly the left pectoral group. At 5:30 A.M.,

the patient was noted to have a spontaneous rhythm of 60 per minute, and the pacemaker was discontinued. He was still rational, though his sensorium was dulled. During the next few hours, periods of ventricular asystole recurred and became more frequent. On the morning of October 6 it was decided to apply the apparatus constantly, and to maintain a dominant rate of 60 beats per minute. We found the required amplitude in this patient to be 50 volts or higher. Sedation, in the form of 100 mg. doses of Demerol, was given as necessary. With time, and this sedation, it was found that the patient's tolerance to the stimuli increased. The pacemaker maintained the arterial pressure at 130/50 mm. Hg. With the stethoscope, the pectoral muscular contractions sounded like the thud of a wooden hammer on the chest wall, and each contraction was followed by a sound of variable loudness which may have been the second sound of the ventricular beat. In measuring the arterial pressure by the auscultatory method, the skeletal muscular contraction was also heard over the brachial artery and was followed by the usual brachial artery sounds. While the patient was maintained entirely by the cardiac pacemaker, no Stokes-Adams attacks occurred, though each time the instrument was turned off for seconds, ventricular asystole appeared. For a period of 12 hours, there were no auricular contractions seen in the electrocardiograms, but these later returned. There was no real change in the patient's level of consciousness with the pacemaker applied, and it was assumed that irreversible cerebral damage had occurred. Cheyne-Stokes respirations also continued, with periods of apnea lasting 10 seconds. The elevated blood sugar was treated with appropriate amounts of insulin, and intravenous therapy was maintained. At 10:30 P.M., October 6, an Adrenalin drip of 4 c.c. of 1/1000 solution in one liter of 5 per cent glucose in water was started at a rate of 15 drops per minute. Ephedrine, 30 mg., was also given intramuscularly. For a total of 63 hours, the patient was thus maintained, and until the last few minutes of life the arterial pressure remained at 130/60 mm. Hg, with an adequate urinary output. Then, at 10:50 A.M., October 8, the patient became cyanosed, totally unresponsive, and one hour later, after a gradual drop in arterial pressure, his respirations ceased. During the last hour of life, progressively greater amplitudes from the pacemaker were necessary to evoke a ventricular contraction, until finally, maximum amplitude of 150 volts produced no ventricular contractions.

An autopsy was performed. The heart weighed 460 grams. The coronary arteries were patent and remarkably free of arteriosclerotic changes for a man of 82 years. There was an old area of fibrosis in the left ventricle, high up and posteriorly, but no fresh or recent areas of infarction were seen. Microscopic examination of the Bundle of His revealed numerous small old scars.

CASE 2.—J.F., a 62-year-old white male, was admitted to the Herbert Reddy Memorial Hospital on Sept. 13, 1954. He had been celebrating at a local night club. At 3 A.M., at the height of the party, he suddenly felt faint and began sweating profusely. He had no chest pain. He was taken home and spent the remainder of the night in a restless and apprenhensive state. In the early morning, he experienced a syncopal attack which lasted one minute. When examined by his physician, Dr. S. Ortenberg, at 9 A.M. he was found to have a regular pulse rate of 30 per minute. An electrocardiogram showed complete auriculoventricular dissociation and right bundle branch block. The arterial pressure was 140/80 mm. Hg. He was admitted to the hospital that same evening.

These syncopal attacks first started in 1947, approximately seven years prior to admission. The first one lasted only a few seconds and occurred while he was entering a taxi. Investigation at that time revealed no abnormality other than a hypersensitive carotid sinus reflex. Between 1947 and 1949, he had six more syncopal attacks, each lasting from one to two minutes and accompanied by loss of consciousness but with no apparent sequelae. In 1950, he was given 15 mg. of ephedrine orally per day, and he remained on this medication for one year. There had been no further syncopal attacks during the last five years. He was a heavy smoker, using about 40 cigarettes per day.

Shortly after his admission, he complained of severe palpitation, and an electrocardiogram revealed paroxysmal ventricular tachycardia, rate 140 per minute. Neither procaine amide nor quinidine was given, and the tachycardia reverted spontaneously and suddenly after five hours to complete A-V dissociation with right bundle branch block, a ventricular rate of 30 per minute, and auricular rate of 100 per minute. This same day, he had three more Stokes-Adams

attacks, each of which lasted two to three minutes. Ephedrine, 50 mg., was given orally, and on this medication the pulse remained 30 per minute until the second hospital day when it increased suddenly to 65 per minute. The electrocardiogram continued to show right bundle branch block with sinus rhythm and first degree heart block. This rhythm persisted for one month, during which time no further syncopal attacks occurred. On October 12, he experienced a Stokes-Adams attack, and this was followed by a bradycardia of 30 per minute. This rhythm continued for 12 hours, and then suddenly increased to 60 per minute. The patient remained asymptomatic for another ten days. During this first month in the hospital, there were no further episodes of chest pain, the sedimentation rate was not increased, and there was no elevation of temperature.

During the night of October 22, he sustained a series of twelve Stokes-Adams attacks, each lasting from 30 seconds to two minutes. These commenced during his sleep at about 3:30 A.M. He was in the midst of a convulsive episode when seen by us in consultation at 9:30 A.M. Syncopal attacks were now occurring every thirty seconds. The pacemaker was applied at this time. The electrical impulses were delivered at a rate of 50 per minute, and an amplitude of 50 volts was

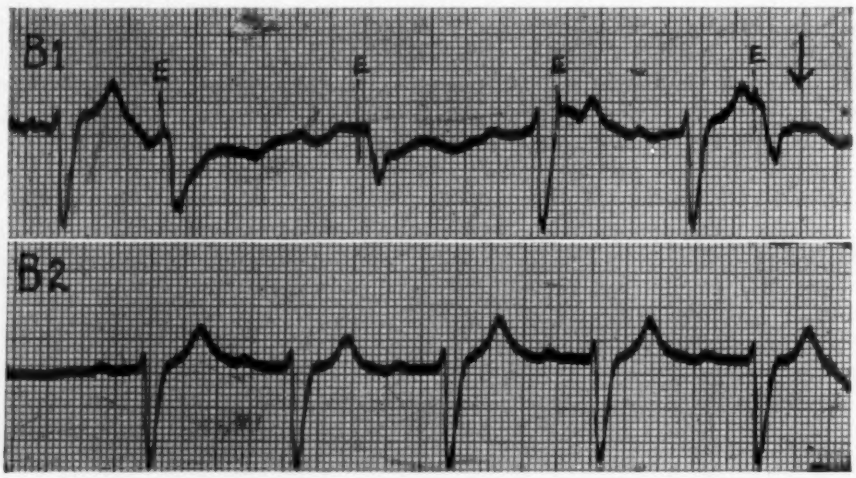


Fig. 2.—Case 2. *B1* **and** *B2*. **Lead aV$_F$. Sinus rhythm beginning to reappear during electrical stimulation (*E*). At arrow, pacemaker discontinued. After a diastolic pause equal to two cardiac cycles, sinus rhythm persisted with P-R interval of 0.30 sec.; as seen in** *B2* **which is a continuation of** *B1*.

necessary to conduct these impulses through the chest wall. During the morning, the pacemaker was discontinued every 20 minutes in order to see whether the patient had resumed normal rhythm. Cessation of artificial electrical stimuli resulted in ventricular asystole and incipient Stokes-Adams attacks. These did not occur while the pacemaker was functioning. All threatened attacks were promptly terminated. While maintained on the apparatus, cerebration was excellent, arterial pressure was constant at 140/80 mm. Hg, and urinary output was adequate. There were no signs of shock. This patient tolerated the muscular contractions well with the aid of Demerol given in doses of 100 mg. about every three hours. Oxygen was not deemed necessary. Intravenous Adrenalin therapy consisting of 4 c.c. of 1/1000 solution in 1 liter of 5 per cent glucose in water was given at a rate of 15 drops per minute in the hope of initiating normal rhythm. Intramuscular ephedrine was also given in 30 mg. doses every four hours. In addition, it was decided to administer cortisone in this case.[6] Chlor-triplon, 50 mg. every four hours, was also given at the request of the referring physician.

He remained dependent on the pacemaker for 10 hours. Occasionally, a few brief runs of idioventricular beats occurred, but these did not last for more than a few seconds and were followed by asystole and threatened syncope if the pacemaker was withheld. After ten hours, however, cessation of electrical stimuli was followed by spontaneous ventricular contractions occurring at a rate of 60 per minute. The electrocardiogram revealed first degree heart block and right

bundle branch block. The pacemaker was not reapplied. The patient was maintained on 100 mg. of cortisone per day, and 15 mg. of ephedrine four times a day by mouth. He remained completely free from Stokes-Adams attacks, and eight days later was discharged from the hospital. During the seven months which have since elapsed, he has resumed his usual work. He had several momentary episodes of faintness in the first three months after discharge but has been completely asymptomatic since.

CASE 3. M.S., a 54-year-old white male, was admitted to the Jewish General Hospital 3:30 P.M. on Dec. 16, 1954, because of sudden loss of consciousness 35 minutes earlier. This man had been in excellent health all his life. He had his first attack of syncope in 1952. This occurred at work without prodromata. He was taken to the emergency room of another hospital where he was observed for several hours and then sent home. No electrocardiograms were recorded. He returned to work the next day and was free from syncopal attacks for the next two years. During this interval he had no cardiac pain, shortness of breath, or orthopnea. On May 16, 1954, while sitting quietly at home, he had another convulsive attack. A physician called to his home administered Coramine and Adrenalin, and within seconds the patient "suddenly came to life." Shortly thereafter, he was admitted to this hospital. During that admission, he was found to have auricular fibrillation which reverted spontaneously to normal sinus rhythm after a few hours. There were no Stokes-Adams attacks. Electrocardiograms showed right bundle branch block. There was no evidence of recent myocardial infarction. After 10 days observation, he was discharged. He was followed in our cardiac clinic after that admission and continued to show right bundle branch block.

He returned to work and was asymptomatic for eight months. While standing in his store on Dec. 16, 1954, he fell to the floor without warning. He had a convulsion and was cyanotic. He arrived at the hospital by ambulance 35 minutes after this first Stokes-Adams attack. During this interval, he was having a convulsion every two to three minutes, and his sensorium was dulled when first seen by us. On admission to the ward, he was semicomatose, respirations were Cheyne-Stokes in nature, and the pulse rate varied from 15 to 60 per minute. About five minutes after admission, he had another Stokes-Adams attack. The arterial pressure was 60/0 mm. Hg. Neosynephrine, 1 c.c., was given intravenously, and Demerol 100 mg. intramuscularly. At the same time, an intravenous Levophed drip was started. The first attack after admission lasted one minute and terminated with a heart rate of 30 per minute. Three minutes later, a second attack ensued. At this point, the pacemaker was applied. Electrical impulses at the rate of 60 per minute were delivered, with an amplitude of 50 volts. These were immediately effective. However, during the first minute, the patient remained semicomatose, and there was no interruption of the apneic phase of the Cheyne-Stokes respirations. Then, after this minute, the sensorium began to clear. After another three minutes, spontaneous beats were seen on the electrocardiogram. At this point, the electrical stimuli were discontinued. The heart rate was 80 per minute and regular, and the arterial pressure 140/75 mm. Hg. This rhythm was maintained for five minutes, when another Stokes-Adams attack occurred. The pacemaker was reapplied for another four minutes. This was followed by the appearance of normal sinus rhythm of 80 per minute, which was maintained until the time of discharge 9 days later.

After his discharge on Dec. 24, 1954, he remained well for one month, during which he received no medication, worked regularly, and was free from any significant signs or symptoms of heart disease. His only complaint was a feeling of lightheadedness when walking uphill or mounting a staircase rapidly. On the evening of Jan. 24, 1955, a few minutes before retiring, he complained of a feeling of nausea and dizziness. He fell asleep, however, and had no syncopal attacks. The next day he continued to feel weak and dizzy, consulted with the referring physician, Dr. Sidney Segall, who advised immediate hospital admission.

The patient was readmitted for the third time on the evening of January 25. Physical examination revealed no gross changes since his last admission one month earlier except for a pulse rate of 35 per minute. The arterial pressure was 115/65 mm. Hg. The admission ECG showed 3:1 heart block and right bundle branch block. The following day, he suddenly developed a syncopal attack while eating his noon meal. The pacemaker was applied and after the attack was terminated, spontaneous beats recurred and persisted for about five hours. Auscultation of the heart

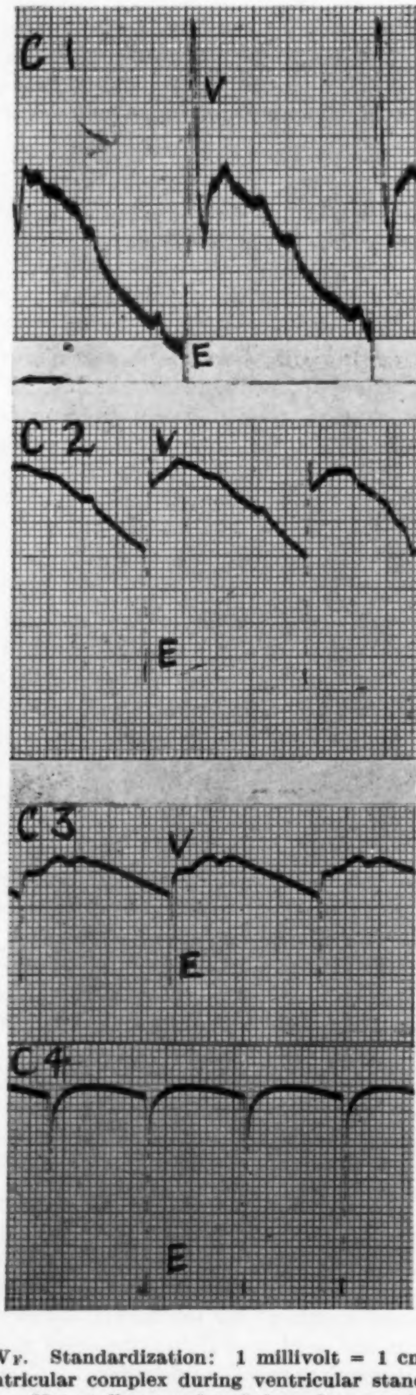


Fig. 3.—Case 3. Lead aV_F. Standardization: 1 millivolt = 1 cm. *E* represents the electrical impulse; *V* represents the ventricular complex during ventricular standstill. *C1*, Jan. 27, 1:15 A.M. Amplitude of stimulus 35 volts. Note tall upward and deep downward deflection of ventricular complex. Blood pressure, 130/65 mm. Hg. *C2*, Feb. 2, 2 A.M. Amplitude of stimulus 40 volts. Note great reduction in amplitude of both deflections of *V*. Blood pressure, 110/70 mm. Hg. *C3*, Feb. 3, 12:30 P.M. Amplitude 75 volts. No apparent initial *V* deflections but suggestion of T wave present. Blood pressure not obtainable, but patient moving. *C4*, Feb. 3. Amplitude 150 volts. Immediately after death at 7:10 P.M. Total absence of *V* deflections and no suggestion of T wave.

at this time revealed the first sound of varying intensity and a split second sound whose second component was a faint short sound as in right bundle branch block. The impression of complete heart block, as compared to the 3:1 block on admission, was confirmed by ECG. There was another Stokes-Adams attack at 5:15 P.M. again terminated by the pacemaker. Auscultation now revealed the first sound constant in intensity and followed by three auricular sounds per beat. The ECG confirmed the impression of 4:1 block. We felt that the syncopal attacks were the result of the change from incomplete heart block to complete A-V dissociation, with ventricular asystole resulting from the failure of the idioventricular focus to initiate the beat after complete block occurred. The patient was given ephedrine intramuscularly in 30 mg. doses but had five more Stokes-Adams attacks on this second hospital day. At 11:30 P.M., following the termination of an attack by the pacemaker, spontaneous beats did not occur, and stimulation had to be continued for the next six hours. During the first day on which the pacemaker was necessary, then, it was applied for a total of 82 minutes on nine separate occasions, and the day ended with the apparatus functioning. Liberal doses of Demerol were given. Tolerance to the stimuli increased with time. During his previous admission this patient had been given stimuli of 50 volt amplitude. On this occasion we found the initial amplitude requirements to be 25 volts. The rate was set at 60 impulses per minute. During the night of January 27, when the pacemaker was continuously applied from 11:30 P.M. to 6:30 A.M., the arterial pressure remained constant at 130/65 mm. Hg. It took 9 to 12 seconds for signs of a Stokes-Adams attack to occur if electrical stimuli were discontinued during this period. At this time, empirically, 200 mg. of cortisone was given parenterally, followed by 100 mg. daily until the time of death. In addition to the intramuscular ephedrine, we also administered Adrenalin in oil intramuscularly and isopropylarterenol (Isuprel) sublingually, 10 mg. doses every four hours. Spontaneous beats appeared early in the morning of January 27, and the pacemaker was discontinued. However, during the day, four more syncopal attacks occurred. One such attack required 75 volts to be terminated. The dominant rhythm varied from 3:1 to 2:1 heart block throughout the rest of his illness, and the appearance of complete heart block occurred less frequently. It was on this second "pacemaker" day during which the apparatus had been in use for a total of 7 hours, that burns began to appear at the site of application of the electrodes. The nursing care had been diligent, and the electrodes had been moved frequently. These burns were to become more severe as the illness progressed. We found that cleansing with a mild antiseptic solution, as well as the application of antibiotic ointment (Aureomycin 1 per cent) was helpful. An oscilloscope screen was set up beside the pacemaker and the electrocardiograph. By the evening of January 27, the patient was resting comfortably without the pacemaker, which had been in operation for a total of 7 hours the second day of its use.

The third day after the initial application of the pacemaker, no Stokes-Adams attacks occurred. There were frequent changes in the degree of block, but the dominant rhythm was a 3:1 block with a rate of 45 per minute. The pacemaker was required again at 3 A.M. on January 29. It was applied continuously for the next 7½ hours, during which no spontaneous ventricular beats were seen. At 10:30 A.M., on January 29, despite the absence of such beats, we discontinued the pacemaker and were surprised to find an idioventricular rhythm of 3:1 at a rate of 48 per minute. This seemed a strange coincidence. The pacemaker was not required again until 4:30 P.M. the next day, January 30. At this time, another Stokes-Adams attack occurred. An amplitude of 50 volts was required to terminate it, and 40 volts to keep the patient free from syncopal attacks. The machine was necessary for the next 7 hours until the patient developed a spontaneous rhythm of 2:1 block with a rate of 60 per minute. He maintained this rhythm for about 45 hours. At 7:50 P.M. on February 1, he developed a Stokes-Adams attack and required the pacemaker continuously until his death 47 hours later. During these last hours of life, the voltage requirements increased sharply, until at 7:00 P.M. on February 3, 150 volts, maximum for the Zoll model pacemaker, did not cause ventricular contraction, and the patient died. Intracardiac Adrenalin was of no avail.

Examination of the heart revealed it to be slightly enlarged, weighing 385 grams. The coronary arteries, as in our first case, grossly, were patent. There were no areas of infarction, old or recent, and except for an area of endocardial thickening in the region of the posterior cusp of the tricuspid valve, and one in the basilar area of the interventricular septum just inferior to

the aortic cusps, the heart might well have been considered grossly normal. Microscopic studies of the area of the Bundle of His are being prepared.

DISCUSSION

Three males, 82, 62, and 54 years of age, respectively, entered the hospital because of Stokes-Adams attacks. These became progressively more frequent and of longer duration and showed no signs of responding predictably to conventional therapy. It was demonstrated that each attack of ventricular arrest could be terminated almost immediately by the application of the Zoll Cardiac Pacemaker. Arterial pressure was adequately maintained in all cases.

The first patient died 63 hours after admission, having reached a point at which electrical stimulation failed to cause the myocardium to respond. Autopsy revealed microscopic areas of fibrosis in the region of the Bundle of His, but no evidence of recent infarction.

The pacemaker was applied continuously for 10 hours in the second case. During this time, despite the concomitant use of Adrenalin, ephedrine, and cortisone, spontaneous beats did not occur in the absence of electrical stimuli from the pacemaker. After the ten-hour period this patient resumed his previous sinus rhythm of 60 beats per minute, with right bundle branch block and first degree heart block. This persisted until the time of his discharge eight days later. At the time of writing, another seven months have elapsed, and he has returned to work as a traveling salesman. He has had no syncopal episodes during the last four months. His family physician has maintained him on cortisone during this interval.

In the third patient, while it is possible that the attack during his second admission might have terminated spontaneously, we were nevertheless able to achieve this immediately with the pacemaker. During that admission, he was thus spared the extra moments of cardiac arrest and consequent cerebral and cardiac hypoxia. During his final admission, he required the pacemaker for a total of more than 70 hours, with the longest single application lasting 47 hours to the time of his death. Examination of the heart revealed no gross abnormalities. Microscopic sections of the Bundle of His are being prepared.

All three cases have certain other features in common. Recent myocardial infarction did not occur in the two who died, nor did the clinical picture suggest it in the patient who survived. The paucity of gross findings at autopsy in these and other cases supports the contention of Parkinson and associates[7] that this condition is probably a disease rather than a syndrome.

Despite good nursing care, we were unable to prevent the occurrence of skin burns at the site of electrode application. We do not think this is a pressure phenomenon. The electrodes were moved frequently, the skin areas were massaged and kept clean, and adequate amounts of electrode jelly were applied. It is more likely that these areas of necrosis are due to electrical arc burns. They can be minimized by the application of antibiotic ointments, but we were unable to prevent their occurrence.

The muscular contractions caused by the stimuli are very painful, and although tolerance to them increases with time, generous use of analgesia in the

form of Demerol was found to be of help. When adequate sedation was given, the patients were able to sleep soundly while the pacemaker was functioning.

In all three cases, but more particularly so in those who died, we found that progressively higher amplitudes were necessary to effect a response. This phenomenon was observed in animals by Lister in 1858 (Quoted in Walshe[1]). Also, the amplitude of current necessary to terminate a Stokes-Adams attack was usually greater than that required to maintain ventricular contractions once such an attack had been stopped. The voltage required to cause ventricular response varies not only from patient to patient but also fluctuates from time to time in any given patient. In fact, our last two cases were able to suggest optimum voltages for themselves. We found it best to start with an amplitude of about 25 volts and then to increase this as necessary.

The projection of the electrocardiogram on the cathode-ray oscilloscope screen was of assistance in the management of the third case. The nursing staff was soon able to predict a Stokes-Adams attack by observing the pattern of the complexes on the screen. This freed them from the necessity of having their fingers on the pulse at all times or watching the conventional electrocardiogram.

When the pacemaker was functioning, clearest tracings on the electrocardiograph were obtained on Lead aV_F, although the standard limb leads could all be recorded. We used the latest Sanborn Viso-Cardiette.

We attempted to increase the independent heart rate during a period of bradycardia in our third case by applying the pacemaker at a rate of 70 impulses per minute. The reasoning was based on the assumption that an increased rate, though artifically induced, might result in improved coronary circulation. If the disturbance in conduction causing the bradycardia were due to ischemia, then more adequate circulation might be expected to improve conduction. However, we were unable to influence the independent heart action in this manner.

We do not think that electrical beats from the pacemaker interfered with the production of intrinsic ventricular rhythm (see Fig. 2, *B1*). The sensorium remained clear if the proper number of effective stimuli were delivered. The optimal rate in our cases was 60 per minute. In the first patient, there had been prolonged cerebral hypoxia and probable damage to higher centers before admission. As a result, his cerebration was poor. However, during the long hours of heart action maintained by the pacemaker, our second and third patients were alert and cooperative.

In studying the electrocardiograms of the two patients who died, we note one common finding (Fig. 3). At the onset of therapy with the pacemaker, the configuration of the complex is identical in the two cases. It is composed of a downward deflection (*E*) which represents the electrical impulse, followed by an upward and downward deflection (*V*) comparable to R and S waves. Finally, there is a long low wave comparable to a T wave. As the clinical condition deteriorated, the ventricular complexes diminished in amplitude and were very low, 6½ hours before death. These changes may be of prognostic significance.

The cardiac pacemaker is an effective and convenient means of terminating

Stokes-Adams attacks. It is very likely that in the second case it was lifesaving. It is obvious that an instrument such as this does not affect the long-term outlook in Stokes-Adams disease, and that the prognosis remains dependent on the underlying etiologic factors. However, this condition may occur over a period of a few days, and then if the patient survives, may not recur for months or years. If the cardiac pacemaker is readily available at a time when these syncopal attacks are at their height, predictable support at this crucial period may result in an indefinite prolongation of life. Our second case illustrates this point. In other circumstances of cardiac arrest, such as anesthetic accidents during surgery, drowning, suffocation—provided the myocardial reserve is unimpaired—this instrument has its greatest value. When conveniently placed in the operating room, its simplicity and ease of operation may obviate the necessity for thoracotomy and cardiac massage.

SUMMARY

Three cases of Stokes-Adams disease are reported. These failed to respond to conventional therapy and were treated for varying periods with the external electric pacemaker. One patient died after 63 hours, a second survived one admission but returned one month later, and died after a total of 70 hours of the pacemaker. A third patient who was without independent ventricular contractions for a period of 10 hours was maintained for that time by means of the pacemaker. He was discharged improved, has returned to work, and now, 7 months later, is still free from Stokes-Adams attacks. The pacemaker was found to be a convenient and practical means of reanimating the arrested heart, with the ultimate prognosis depending on the underlying etiologic factors disturbing the conducting mechanism.

The technique and complications arising out of the use of the pacemaker are also discussed.

SUMMARIO IN INTERLINGUA

Es reportate tres casos del morbo Stokes-Adams que non respondeva a therapias conventional e que esseva tactate durante varie periodos per medio del pacemaker electrico-externe. Un patiente moriva post 63 horas de tal tractamento. Un secunde patiente superviveva su prime hospitalisation. Un mense plus tarde ille esseva re-admittite e moriva post un total de 70 horas de application del pacemaker electric. Un tertie patiente esseva mantenite per medio del pacemaker durante un periodo de 10 horas sin independente contractiones ventricular. Ille esseva dimittite in condition meliorate. Ille retornava a su labor e ha remanite usque hodie, i.e. durante un periodo de 7 menses, libere de attaccos Stokes-Adams. Nos trovava que le pacemaker es un utile e practic medio pro reanimar le corde arrestate. Le ultime prognose depende del natura del subjacente factores etiologic que ha disturbate le mechanismo conductori.

Es discutite le technica del pacemaker e alicun complicationes que resulta de su uso.

ADDENDUM

After this paper was submitted for publication, two additional patients were treated with the pacemaker. One patient, a man aged 79, under treatment at the Queen Mary Veterans' Hospital for arteriosclerotic heart disease, congestive cardiac failure, and chronic lymphatic

leukemia, developed a series of Stokes-Adams attacks. At first these were brief and ended spontaneously. The pacemaker was applied for a total of 45 hours in the course of three days. Molar sodium lactate was given, but sustained idioventricular rhythm did not begin until 6 hours after this therapy. The patient remained free of Stokes-Adams attacks for 35 days, then the pacemaker was required again briefly. This case is more fully reported elsewhere in this issue. The second patient, a man aged 72, had been observed by one of us (H.N.S.) for 24 years, during which he had symptoms and signs of arteriosclerotic coronary artery disease. He had had Stokes-Adams attacks in 1947 and in 1954. These were brief and terminated spontaneously. He was admitted in a state of profound shock; Levophed intravenously and the pacemaker were applied immediately. The electrocardiogram showed complete A-V dissociation. He lived for only ten minutes after admission. Autopsy revealed fresh thrombotic occlusion of the anterior descending branch of the left coronary artery and of the right circumflex coronary artery near its origin. His death was attributed to irreversible shock.

REFERENCES

1. Walshe, W. H.: A Practical Treatise on the Diseases of the Heart and Great Vessels, Philadelphia, 1862, Blanchard & Lea, p. 155.
2. Hyman, A. S.: Resuscitation of the Stopped Heart by Intracardial Therapy, Arch. Int. Med. **50**:283, 1932.
3. Callaghan, J. C., and Bigelow, W. G.: An Electrical Artificial Pacemaker For Standstill of the Heart, Ann. Surg. **124**:8, 1951.
4. Zoll, P. M.: Resuscitation of the Heart in Ventricular Standstill by External Electric Stimulation, New England J. Med. **247**:768, 1952.
5. Zoll, P. M., Linenthal, A. J., Norman, L. R., and Belgard, A. H.: Treatment of Stokes-Adams Disease by External Electric Stimulation of the Heart, Circulation **9**:482, 1954.
6. Zoll, P. M.: Personal communication, Oct. 20, 1954.
7. Parkinson, J., Papp, C., and Evans, W.: The Electrocardiogram of the Stokes-Adams Attack, Brit. Heart J. **3**:171, 1941.

ADRENAL STEROIDS AND AURICULOVENTRICULAR CONDUCTION

BERNARD LOWN, M.D., WALTER L. ARONS, M.D., WILLIAM F. GANONG, M.D., JEHANGIR P. VAZIFDAR, M.D., AND SAMUEL A. LEVINE, M.D.

BOSTON, MASS.

THE P-R interval of the electrocardiogram measures the duration between the inception of auricular and ventricular depolarizations. This interval consists of two components: a fixed conduction time for the passage of the excitation wave along the auricle and an inconstant delay at the junctional tissue. The impulse traverses auricular muscle rapidly. Transmission from the S-A to the A-V node consumes less than 0.07 sec.[1] Changes in the length of the P-R interval are due to a variable delay of the stimulus in the A-V node. Nodal delay augments ventricular efficiency both by permitting completion of auricular systole with maximum ventricular filling before contraction and by favoring complete recovery of all muscle bundles from the preceding impulse. There is a structural and functional basis for the delay. The small diameter of the fibers in the node and their irregularly winding course suggest a structural adaptation for diminished conduction velocity. A variable period of latency constitutes the functional basis of the delay.[2]

A multiplicity of factors influences the duration of the functional delay at the A-V node. Among the most important are autonomic nervous stimuli and the action of drugs. The role of endocrine factors in determining the duration of A-V conduction has not been recognized. In a recent study in which large populations were divided on the basis of the A-V conduction time, it was observed that patients with Addison's disease were mainly limited to the group with long P-R intervals, while patients receiving cortisone were exclusively found in the population with short P-R intervals.[3] The object of the present study is twofold: first, to determine whether deficiency and excess in production of adrenal cortical hormone, as represented by patients with Addison's disease on the one hand and Cushing's disease on the other, are associated with differing P-R durations; secondly, if such changes do occur, to isolate the possible causative factors.

MATERIAL AND METHODS

P-R intervals were measured in 927 electrocardiograms. Of this number 219 electrocardiograms were obtained from fifty subjects with proved Addison's disease, 169 from thirty-four patients with well-established Cushing's syndrome, and 539 constituting the control group from normal individuals without apparent endocrine or cardiovascular disorders. Records of twenty-four of the patients with Cushing's syndrome were obtained from files of the Massachusetts General

From the Department of Medicine, Harvard Medical School, and the Peter Bent Brigham Hospital, Boston, Mass.

Received for publication April 22, 1955.

Hospital,* the remainder from the records of the Peter Bent Brigham Hospital. There was a marked preponderance of the female sex in the group with Cushing's syndrome with only six males among the thirty-four patients. In the group with Addison's disease, twenty-nine of the fifty were females.

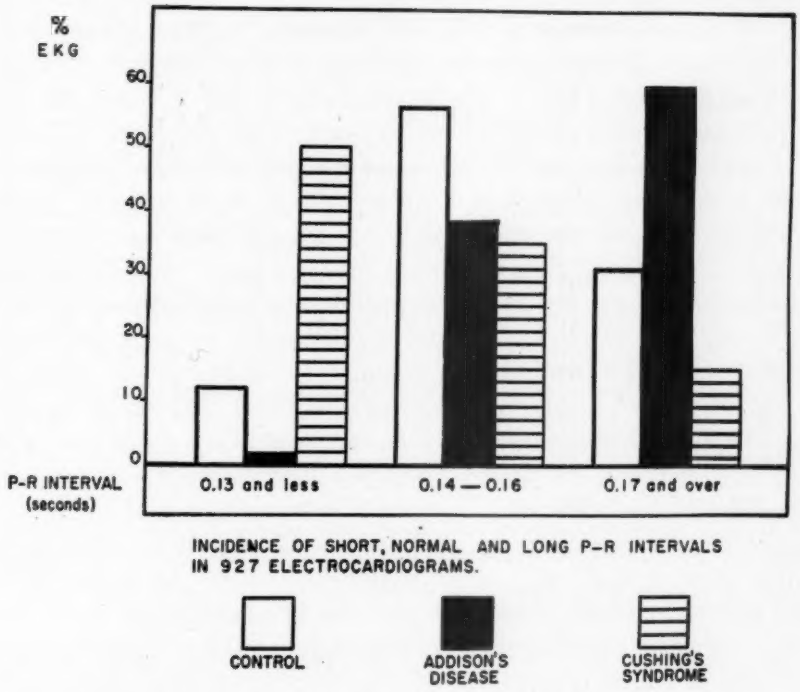


Fig. 1.

P-R interval duration was measured in Lead II. In those instances in which the electrocardiogram exhibited a Q_1 balanced by an R_3, or an R_1 balanced by a Q_3, the correct interval was determined either in Lead III or by subtracting the longest QRS duration from the longest P-R interval.[4] Patients with heart rates exceeding 100 beats per minute in all available tracings were excluded from this study. Patients with Addison's disease who were receiving cortisone or who were on maintenance digitalis therapy were also eliminated.

RESULTS

The distribution of P-R intervals according to their duration in 927 electrocardiograms in the three populations is represented and itemized in Fig. 1 and Table I. The mean values for the control, Addison's, and Cushing's groups were 0.158, 0.176, and 0.136 sec., respectively. The distribution of P-R intervals and the mean duration for the entire control group were similar to those reported by others for normal individuals.[5,6] Statistical analysis shows the data to be highly significant. Analysis of the distribution of P-R interval durations in the three populations by means of the Chi-square method demonstrates a

*These patients were kindly made available for study by Dr. Fuller Albright.

TABLE I. P-R DISTRIBUTION IN 927 ELECTROCARDIOGRAMS DERIVED FROM THREE GROUPS OF PATIENTS: (1) 50 CASES OF ADDISON'S DISEASE, (2) 34 CASES OF CUSHING'S DISEASE, AND (3) 539 NORMAL CONTROLS

P-R DURATION (SECOND)	NORMAL		ADDISON'S DISEASE		CUSHING'S SYNDROME	
	NUMBER	%	NUMBER	%	NUMBER	%
0.12 and less	34	12.0	0	1.9	55	50.1
0.13	41		4		30	
0.14	62	56.5	26	38.0	10	35.0
0.15	78		22		34	
0.16	164		35		15	
0.17	41	31.5	31	60.1	15	14.9
0.18	66		31		6	
0.19	26		35		0	
0.20 and over	27		35		4	
Total No. of EKG's	539		219		169	
Mean P-R	0.158		0.176		0.136	

value for P of less than 0.001. In 86 per cent of the patients with Addison's disease the P-R interval exceeded 0.14 sec. Only one patient had a relatively short P-R interval. In this patient, the P-R averaged 0.13 sec. in four tracings, and the degree of adrenal insufficiency was mild. First-degree heart block was present in 20 per cent of the Addisonian patients during some stage of their disease. Approximately 75 per cent of the patients with Cushing's syndrome had P-R intervals measuring less than 0.15 sec. In only one patient was the P-R interval longer than 0.18 sec., but in this patient the electrocardiogram showed the characteristic changes of a previous posterior myocardial infarction.

The patients with Addison's and Cushing's diseases were comparable as regards age. The average in the former was 39 years, while in the latter it was 36 years. Electrocardiographic derangements were noted in 60 per cent of the patients of each group. No difference in P-R duration was observed in Cushing patients having either normal or abnormal tracings. Among the Addisonian patients those with deranged electrocardiograms had a slightly longer conduction duration. Acceleration of heart rate did not affect the P-R interval in a predictable manner in either group. In some patients with Addison's disease significant increases in heart rate were accompanied by further lengthening of A-V conduction, at times with emergence of first-degree heart block. In one patient a rate increase from 82 to 130 was associated with a P-R change from 0.20 to 0.23 sec.

ADDISON'S DISEASE

What are the factors which cause or contribute to the prolongation of A-V conduction in Addison's disease? The increased incidence of first-degree heart block has been noted previously as one of the possible derangements accompanying adrenal insufficiency.[7,8] A comprehensive study of the electrocardiogram in 90 patients with Addison's disease has been reported recently by Somerville and associates.[9] In order of frequency the major alterations consisted of flattening or mild inversion of the T waves especially in the precordial leads, prolongation of the Q-T interval, low voltage of the QRS complex in the standard limb leads, first-degree heart block (14.5 per cent of the patients), widening of the QRS complex, and S-T segment depression. These electrocardiographic changes were unrelated to age and heart size. They remained unaffected by prolonged DCA administration. These authors found no significant electrocardiographic changes during or shortly after Addisonian crisis. Since crisis is characterized by profound alteration in electrolyte balance, they concluded that disturbance of adrenal cortical regulation of mineral metabolism was not the responsible factor accounting for the deranged electrocardiogram.

Somerville and co-workers found that hypometabolism was a contributory factor. Patients with basal metabolic rates below the range of -10 to -19 per cent had an increased incidence of electrocardiographic abnormality.[9] In our fifty patients with Addison's disease no relation was evident between the state of thyroid function and A-V conduction time. In twenty-seven patients the duration of the P-R interval did not correlate with the level of the radioactive iodine uptake gradient, and in sixteen patients the interval was the same whether the basal metabolic rate was less than -19 per cent or over -5 per cent. The observed association of prolonged A-V conduction in myxedema may therefore be due to depression of adrenal cortical function known to occur in hypothyroidism.

Somerville and co-workers observed that abnormal tracings generally were associated with the lowest adrenocortical potential as measured by the rate of urinary 17-ketosteroid excretion and the Thorn test. They found electrocardiographic abnormality to be twice as frequent among females. The administration of cortisone, while having no effect on the normal Addisonian electrocardiogram, caused improvement in ten of twelve patients who had abnormal tracings. In one patient with first-degree heart block normal conduction was restored.[9] In our series of patients with Addison's disease, the P-R interval was slightly longer in females than in males. Sixteen of our patients received cortisone. In nine, significant abbreviation of the P-R interval, ranging from 0.02 to 0.05 sec., was noted. The degree of shortening was related to the length of the P-T interval prior to therapy. Patients with the longest intervals exhibited the most change.

CUSHING'S SYNDROME

Patients with Cushing's disease do not have specific electrocardiographic patterns. Changes in the electrocardiogram have been usually attributed to coexisting hypertension or to disturbed electrolyte balance. The present study

demonstrates significant difference in the duration of A-V conduction (averaging 0.04 sec.) between groups of patients with Cushing's and Addison's diseases. Additional electrocardiographic distinctions were noted between the two groups. Five patients with Cushing's disease exhibited frequent auricular or ventricular extrasystoles. Two others had bouts of nodal tachycardia, and three showed a wide slurring ascent of the QRS complex similar to that which occurs in the Wolff-Parkinson-White syndrome. No such manifestations were observed among the fifty patients with Addison's disease.

What factors contribute to the accelerated auriculoventricular conduction in Cushing's disease? Hypertension is believed to predispose to a shortened P-R interval[10] but when the patients with Cushing's syndrome were divided into two groups on the basis of the presence or absence of left ventricular hypertrophy pattern, no difference in the duration of the P-R interval was evident. There was an equal distribution of patients with normal and abnormal electrocardiograms in the short and normal P-R categories (Table II). No relation was observed between the rapidity of A-V conduction and the state of thyroid function as measured by the basal metabolic rate and the radioactive iodine uptake. A difference in A-V conduction was noted on the basis of sex. Five of the six males, in all of whom the underlying pathology was adrenal cortical hyperplasia, had P-R intervals of 0.12 sec. or less.

TABLE II. RELATION OF P-R DURATION TO THE ELECTROCARDIOGRAPHIC PATTERN IN 34 PATIENTS WITH CUSHING'S SYNDROME

ELECTROCARDIOGRAM	SHORT P-R 0.13 SECOND AND LESS		NORMAL P-R 0.14 SECOND AND OVER	
Normal	7		5	
Abnormal	10		12	
Breakdown of abnormal EKG's	L.V.H.	6	L.V.H.	5
	N.S.T.C.	3	N.S.T.C.	4
	M.I.	1	M.I.	3

L.V.H.=Left venticular hypertrophy.
N.S.T.C.=Nonspecific T-wave change.
M.I.=Myocardial infarction.

The urinary excretion of 17-ketosteroids was the one measure of adrenal cortical function available in nearly all the patients. Glucocorticoids would have been a better reference, but at the time of this study were not available. Data were obtained in thirty-two patients and are summarized in Table III. Patients with normal and abnormal electrocardiograms showed the same levels of excretion. A significant difference in urinary 17-ketosteroid concentration was noted when patients were divided into two groups on the basis of the P-R duration. The average amount excreted was 22.0 mg. in 24 hours for the group with a short interval compared to 10.1 mg. for the group with a normal interval. This correlation only held for each group as a whole. There were individual

instances of short conduction and low excretion as well as some showing a converse relationship.

TABLE III. RELATION OF URINARY 17-KETOSTEROID EXCRETION TO THE INCIDENCE OF ELECTROCARDIOGRAPHIC ABNORMALITIES AND P-R INTERVAL DURATION

	ELECTROCARDIOGRAM		P-R DURATION (SECOND)	
	NORMAL	ABNORMAL	0.13 AND LESS	0.14 AND OVER
Number of patients	12	20	15	17
Mean 17-ketosteroid excretion (mg./24 hr.)	16.0	15.4	22.0	10.1

Thirty-two of the thirty-four patients with Cushing's disease were subjected to exploration; in all the glandular histology was established. Fifteen patients were found to have hyperplasia, eight had adenomas, six had normal adrenals, and three had carcinomas. Of interest is the fact that patients with cortical hyperplasia had predominantly short P-R intervals, while those with adenomas had normal P-R intervals (Table IV). This was but an extension of the observation relating A-V conduction duration to the 17-ketosteroid excretion data. The average 24-hour excretion value was 5.8 mg. in patients with adenoma compared to 19.6 mg. for the group with hyperplasia.

In fifteen patients, electrocardiograms were available before and after subtotal or complete adrenalectomy. Following surgery, varying regimens of adrenal substitution therapy were employed. In four of the fifteen patients, A-V conduction lengthened by 0.02 sec. or more. Urinary 17-ketosteroid excretion data were available for these four as well as for seven of the eleven patients who demonstrated no change in the P-R duration (Table V). Following adrenalectomy, the decline in 17-ketosteroid excretion averaged 83 per cent when the P-R lengthened, compared to a decline of 41 per cent when it remained constant. The most marked alteration was observed in a patient with cortical hyperplasia. After a subtotal adrenalectomy, the P-R interval increased from 0.12 to 0.21 sec. and both the 17-ketosteroid and C11-oxysteroid excretions were significantly reduced. The former decreased from 13.8 to 0.7 mg. while the latter from 3.5 to 0.225 mg. per 24 hours.

DISCUSSION

In Addison's disease auriculoventricular conduction tends to be prolonged. This is indicated by the paucity of patients with P-R durations under 0.14 sec. and by the high incidence of heart block in this group. Ten of the fifty patients with Addison's disease reported here had conduction impairment at some phase of their illness. In addition a significant number had conduction values bordering on heart block. Sex was not a determining factor. Mineral metabolic derangements were not implicated. The administration of DCA did not appear to contribute to the prolongation. A-V conduction was abbreviated consistently

only by cortisone therapy. These observations suggest that the lengthened P-R interval in adrenal insufficiency is related to the deficiency of C11-oxysteroids.

TABLE IV. RELATION OF P-R INTERVAL DURATION TO ADRENAL CORTICAL PATHOLOGY

ADRENAL CORTICAL MORPHOLOGY	P-R DURATION (SECOND)		
	0.13 AND LESS	0.14-0.16	0.17 AND OVER
Hyperplasia	12	1*	2†
Adenoma	0	8	0
Normal	2	2	2
Carcinoma	2	1	0
Undetermined	1	1	0
Total	17	13	4

*Digitoxin maintenance. Low 17-ketosteroid excretion. (3.0 mg./24 hrs.)
†Both patients had previous posterior myocardial infarctions and one had extensive radiation to the pituitary.

TABLE V. THE EFFECTS OF PARTIAL OR TOTAL ADRENALECTOMY ON THE URINARY 17-KETOSTEROID EXCRETION AND P-R INTERVAL DURATION

P-R DURATION (SECOND)	NUMBER OF PATIENTS	PROLONGATION OF P-R			NO CHANGE IN P-R		
		NUMBER	17-KETOSTEROID EXCRETION—MG./24 HR.		NUMBER	17-KETOSTEROID EXCRETION—MG./24 HR.	
			BEFORE	AFTER		BEFORE	AFTER
0.13 and less	9	3	20.7	2.7	6*	28.2	17.0
0.14 and over	6	1	14.6	5.0	5†	5.6	2.5

*17-Ketosteroid data available in four patients.
†17-Ketosteroid data available in three patients.

Cortisone is known to shorten A-V conduction even when there is no manifest deficiency of adrenal steroids. Massell reports that 82 per cent of the sixty-six patients with heart block due to rheumatic carditis responded to steroid therapy with normalization of conduction.[11] The recently issued report on the treatment of acute rheumatic fever in children with either hormones or aspirin confirms the action of adrenal steroids in decreasing the duration of the P-R interval.[12] In the group receiving hormones, the P-R intervals were shorter during the acute illness than a year later when patients had recovered. The authors suggest that the hormones may exert a direct effect on the atrioventricular conduction time. Abbreviation of prolonged P-R intervals in patients with acute rheumatic fever while being treated with adrenocortical

hormones is therefore no index of abatement or control of the underlying disease process.

Shortening of the P-R interval had been reported to occur during cortisone administration when no rheumatic inflammatory lesions existed in the myocardium.[13] Cortisone also appears to decrease the P-R duration in the absence of heart disease. In a study previously referred to, among 200 patients with P-R durations of 0.12 sec. or less, there were nine patients without heart conditions who were receiving either cortisone or ACTH.[3] There were no patients on steroid therapy among a similar population of 200 with P-R intervals measuring 0.16 and 0.18 sec.

The occurrence in two patients with Cushing's disease of bouts of supraventricular tachycardia is in accord with the shortened A-V conduction encountered in this condition. When the P-R interval measures 0.12 sec. or less and the QRS complex is of normal configuration, a 10 per cent incidence of paroxysmal rapid heart action has been reported.[3] The finding of a slurring of the initial ascending limb of the QRS in three other patients with Cushing's disease is also consistent with the presence of accelerated A-V conduction. Such deformity of ventricular depolarization is a characteristic feature of the Wolff-Parkinson-White syndrome where P-R intervals invariably measure less than 0.12 sec.

The conditions which are reported to be associated with shortened A-V conduction are known to exert potent stress on the adaptive processes of the body. An increased frequency of hypertension and thyrotoxicosis has been reported among patients exhibiting short P-R intervals.[10,14] We have noted that 25 per cent of patients with acute myocardial infarctions, during the first week of illness, have transient shortening of A-V conduction time to levels of 0.12 to 0.13 sec.[3] In patients with Cushing's disease the decrease in P-R is not related either to the state of thyroid function or to the presence of hypertension. It does reflect the degree of hyperfunctioning of the adrenal cortex especially when the underlying pathology is that of hyperplasia.

The autonomic nervous system is believed to regulate A-V conduction duration in health. It is fairly well established that sympathetic stimulation is associated with a shortening, while parasympathetic stimulation with a lengthening of conduction time. The P-R interval is altered most frequently by changes in heart rate. This occurs only when heart rate change is effected by nervous influences.[5] Acceleration of the heart in experimental animals achieved by heating the sinus node or by altering the rate of electrical stimulation does not cause shortening but may even lengthen the P-R interval.[2] Exercise reduces the conduction time, but the shortening is greater than would correspond to the elevated heart rate. Standing which increases sympathetic tone shortens the P-R interval without a change in heart rate. This occurs whether conduction is normal or impaired.[15,16] Thus stimulation of the autonomic nervous system can selectively alter the functional delay at the junctional tissue.

The evidence presented indicates that both autonomic and endocrine factors affect the duration of A-V conduction. Recent studies point to an adrenocortical steroid-neurohumor interaction at the effector level as a widespread phenomenon

in many biologic reactions.[17] A copermissive action between epinepherine and C11-oxysteroids has been shown in the production of eosinopenia,[18] in the mobilization of fat,[19] and in the control of vasomotor tone.[17] DCA did not appear to be an essential participant in these reactions. A similar mechanism may operate in the control of A-V conduction. It may be that the C11-oxysteroids induce alterations in the metabolism of the junctional tissue which condition the response to sympathetic discharge. With normal oxysteroid production A-V conduction responds to autonomic nervous regulation. In the presence of hormone deficiency or overproduction, as in Addison's and Cushing's diseases, the A-V node may be under or overactive. In this regard, it is interesting that the hypothalamus serves as a center for regulating both the sympathetic nervous system,[20] and the pituitary release of adrenocorticotrophin.[21]

These observations may have some pertinence in the care of patients with heart block and Adams-Stokes disease. A theoretic rational is provided for the utilization of a combination of cortisone and sympathomimetic agents for the dissolution of auriculoventricular conduction defect.

SUMMARY AND CONCLUSIONS

1. Adrenocortical hormones participate in determining the duration of A-V conduction. The P-R interval was prolonged in Addison's disease and short in Cushing's syndrome as compared to a normal control population.

2. Ten of fifty patients with Addison's disease exhibited heart block and in only one was the P-R less than 0.13 sec. The mean P-R duration for the group, based on 219 electrocardiograms, was 0.176 sec. compared to a control value of 0.158 sec. in 539 control subjects.

3. In seventeen of thirty-four patients with Cushing's syndrome the P-R was 0.13 sec. or less, in only one patient did it exceed 0.18 sec. The mean P-R duration for the group, based on 169 electrocardiograms, was 0.136 sec.

4. The A-V conduction time in patients with Cushing's syndrome correlated with the urinary 17-ketosteroid excretion and with a finding at surgery of adrenocortical hyperplasia.

5. Since cortisone administration shortens the P-R interval, it is suggested that the C11-oxysteroids participate in the regulation of A-V conduction. Thus this would represent an additional example of the biologic cooperation between adrenocortical steroids and the sympathetic nervous system.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

1. Le objectivos del presente studio es (a) determinar si deficientia e excesso in le production de hormon adrenocortical—representate de un latere per patientes con morbo de Addison, e del altere latere per patientes con morbo de Cushing—es associate con differente durationes del intervallo P-R, e (b), in caso de si, isolar le possibile factores causative.

2. Esseva constatate que le hormones adrenocortical participa in determinar le duration del conduction auriculoventricular. Le intervallo P-R se monstrava prolongate in morbo de Addison e breve in le syndrome de Cushing in comparation con un normal population de controlo.

3. Bloco cardiac esseva exhibite per 10 ex 50 patientes con morbo de Addi-

son. In solo un patiente de iste gruppo le intervallo P-R esseva minus que 0,13 sec. Le median duration P-R pro le integre gruppo, determinate super le base de 219 electrocardiogrammas, esseva 0,176 sec. Pro le 539 individuos del gruppo de controlo le correspondente valor esseva 0,158 sec.

4. In 17 ex 34 patientes con syndrome de Cushing le duration del intervallo P-R esseva 0,13 sec o minus. In solo un patiente, illo excedeva 0,18 sec. Le duration median de P-R in le integre gruppo—basate super 169 electrocardiogrammas—esseva 0,136 sec.

5. In le patientes con syndrome de Cushing le tempore de conduction auriculoventricular esseva in correlation con le excretion urinari de 17-cetosteroides e con le constatation chirurgic de hyperplasia adrenocortical.

6. Proque le administration de cortisona accurta le intervallo P-R, nos opina que le C11-oxysteroides participa in le regulation del conduction auriculoventricular. Isto representarea un exemplo additional del cooperation biologic inter le steroides adrenocortical e le systema de nervos sympathic.

The authors gratefully acknowledge the criticism given by Dr. George W. Thorn.

REFERENCES

1. Prinzmetal, M., and Others: Accelerated Conduction. The Wolff-Parkinson-White Syndrome and Related Conditions, New York, 1952, Grune & Stratton, Inc.
2. Lepeschkin, E.: Modern Electrocardiography, Baltimore, 1951, William and Wilkins Company, vol. 1.
3. Lown, B., Ganong, W. F., and Levine, S. A.: The Syndrome of Short P-R Interval, Normal QRS Complex and Paroxysmal Rapid Heart Action, Circulation **5**:693, 1952.
4. White, P. D., Leach, C. E., and Foote, S. A.: Errors in Measurement of the P-R (P-Q) Interval and QRS Duration in the Electrocardiogram, Am. Heart J. **22**:321, 1941.
5. Ashman, R., and Hull, E.: Essentials of Electrocardiography, ed. 2, New York, 1941, The Macmillan Company.
6. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiogram Obtained From 1,000 Young Healthy Aviators, Am. Heart J. **27**:524, 1944.
7. Coelho, E.: Le coeur dans la maladie d'Addison etude electrocardiographique, Bull. et mém. Soc. méd. d. hôp. de Paris. **48**:280, 1932.
8. Thorn, G. W., Dorrance, S. S., and Day, E.: Addison's Disease; Evaluation of Synthetic Desoxycorterone Acetate Therapy in 158 Patients, Ann. Int. Med. **16**:1053, 1942.
9. Somerville, W., Levine, H. D., and Thorn, G. W.: The Electrocardiogram in Addison's Disease, Medicine **30**:43, 1951.
10. Scherf, D.: The Short P-R Interval and its Occurrence in Hypertension, Bull. New York M. Coll. **4**:115, 1941.
11. Massell, B. F.: ACTH and Cortisone Therapy in Rheumatic Fever and Rheumatic Carditis, New England J. Med. **251**:221, 1954.
12. U. K. and U. S. Joint Report on Rheumatic Fever, Circulation **11**:343, 1955.
13. Hein, G. E., and Whipple, G. H.: The Cardiovascular System in Patients Receiving Cortisone, Veterans Admin. Conf. on Cortisone Research, Aug. 15-16, 1950, p. 17.
14. Söderstrom, N.: Observations on the Significance of Shortened P-R Intervals in the Electrocardiogram, Cardiologia **7**:1, 1943.
15. Manning, G. W., and Stewart, C. B.: Alteration of P-R Interval Associated With Change in Posture, Am. Heart J. **20**:109, 1945.
16. Scherf, D., and Dix, J. H.: The Effects of Posture on A-V Conduction, Am. Heart J. **43**:494, 1953.
17. Levine, R., Goldstein, M., Ramey, E. R., and Fritz, I.: Studies on the Mode of Action of Cortisone in Stress, Bull. New England M. Center **13**:114, 1951.
18. Henry, W. L., Jr., Oliver, L., and Ramey, E. R.: Relationship Between Actions of Adrenocortical Steroids and Adrenomedullary Hormones in the Production of Eosinopenia, Am. J. Physiol. **174**:455, 1953.
19. Wool, I. G., and Goldstein, M. S.: Role of Neurohumor in the Action of the Adrenal Cortical Steroids; Mobilization of Fat, Am. J. Physiol. **175**:303, 1953.
20. Bronk, D. W., Levy, F. H., and Larrabbee, M. G.: The Hypothalamic Control of Sympathetic Rhythms, Am. J. Physiol. **116**:15, 1936.
21. Hume, D. M., and Wittenstein, G. J.: The Relationship of Hypothalamus to Pituitary Adrenocortical Function. In Proc. First Clinical ACTH Conference (Mote, J. R. Ed.). Philadelphia, 1950, The Blakiston Company, p. 134.

Clinical Reports

PAROXYSMAL NODAL TACHYCARDIA WITH RETROGRADE HEART BLOCK, RECIPROCAL RHYTHM, AND BLOCKED RECIPROCAL BEATS

AGUSTIN CASTELLANOS, JR., M.D., RUBEN LOPEZ TOCA, M.D.,
LUIS AZAN, M.D., AND JOSE M. CALVIÑO, M.D.

HAVANA, CUBA

NODAL tachycardia exhibiting retrograde heart block seems to be an infrequent rhythm. Since few cases have been reported in medical literature,[1-3] it was thought of interest to describe the findings on a patient who on several occasions presented electrocardiographic records of nodal tachycardia with retrograde heart block and dropped retrograde auricular beats (Wenckebach's phenomenon), besides reciprocal rhythm and occasional blocked re-entry.

CASE REPORT

M.N., a 62-year-old Negro, was admitted to our service with a history of pulmonary emphysema, air hunger, palpitations, and precordial pain on several occasions.

An electrocardiogram (Fig. 1) taken on the day of admission shows extensive anterolateral ischemia and signs of left ventricular hypertrophy.

The sinus rhythm seems to be interrupted by premature beats, with fixed coupling, the morphology of which is somewhat different from the basic rhythm, and its duration never exceeds 0.06 sec., with an inverted P wave where the R wave returned to the zero line. Therefore, we considered such premature beats (extrasystoles) as belonging to the nodal type with some aberration, and a retrograde stimulation of the auricles, following a ventricular stimulation.

The compensatory pause of the extrasystoles was not complete. The electrocardiographic records performed during the course showed periods of rapid, regular rhythm with a frequency of 140 per minute, and with ventricular complexes quite similar to the extrasystoles found on the day of admission.

A diagnosis of nodal tachycardia was made with aberrant ventricular complexes and with posterior stimulation of the auricles (retrograde conduction) (Fig. 2). This rapid rhythm was seen in the form of short periods, intercalated in periods of sinus rhythm.

Also present during the crisis of tachycardia were retrograde heart block with dropped retrograde auricular beats, some beats of reciprocal rhythm quite similar to the case presented by Drury,[1] and the presence of an obvious irregularity of the ventricular cycles.

Retrograde Heart Block.—In Fig. 3, an electrocardiographic record shows how the P waves are detaching themselves from the ventricular complexes until they reach an R-P of 0.20 sec., and at the same time there is a missed auricular beat, as is seen in cases of blocked re-entry and Wenckebach's phenomenon. Whenever there is a dropped auricular beat the consecutive auricular stimulation shows a very short R-P, not more than 0.08 sec. This type of retrograde heart

From the Service of Clinical Pathology and Clinical Medicine, University Hospital, Havana, Cuba.
Received for publication Dec. 3, 1954.

block has been reported quite frequently in cases of nodal bradycardia,[4] since White[5] published the first case, but we have found only three instances of high frequency nodal rhythm in medical literature. A retrograde heart block can also be seen in Figs. 4 and 5.

Reciprocal Rhythm.—On some occasions, and always corresponding to the longest R-P, there are some beats, the morphology of which is similar to those seen in paroxysmal tachycardia (Fig. 3, middle tracing; Fig. 5, upper tracing). We consider such beats the result of a re-entry stimulus

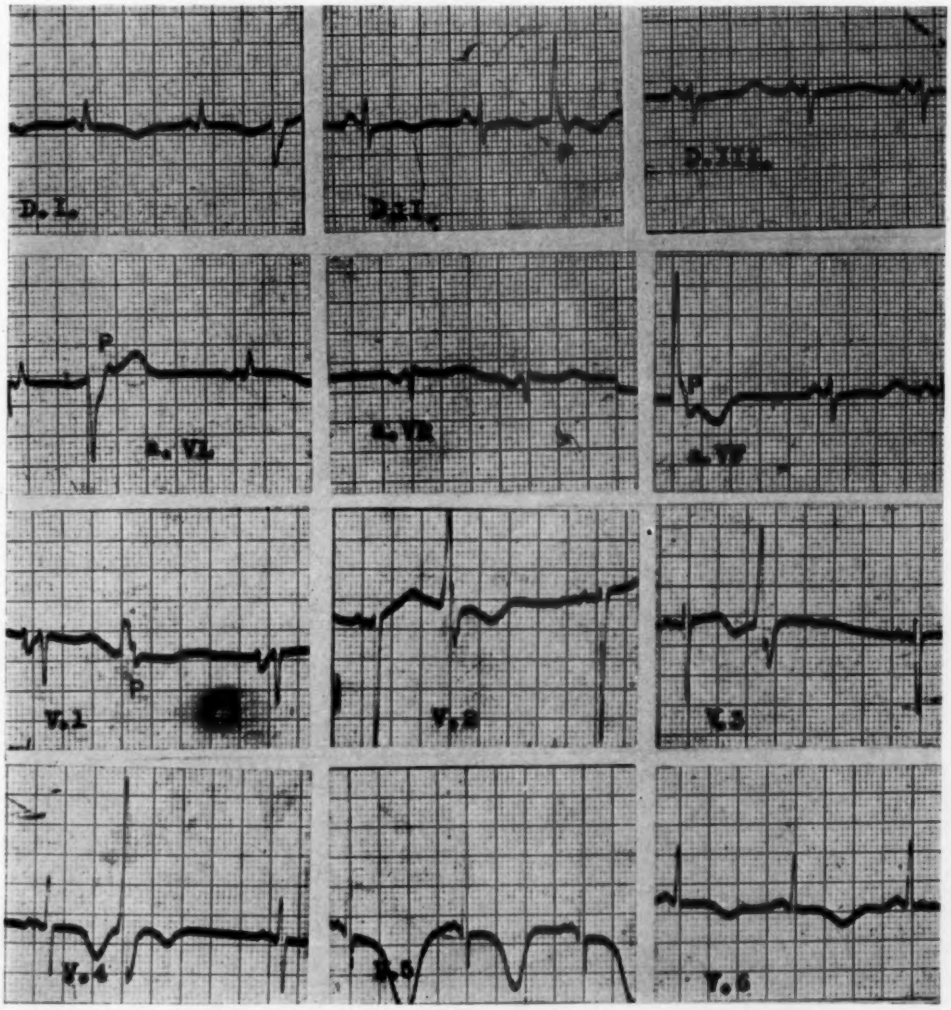


Fig. 1.—Electrocardiogram on admission. Nodal premature beats with aberrant conduction and retrograde stimulation of the auricles, with P waves posterior to the ventricular complexes.

which finds the node and ventricle out of their refractory period. Nevertheless, the retrograde stimuli of these contractions would be blocked. The R-R cycles of these reciprocal beats change very little because they correspond to progressively lengthened R-P (0.24 and 0.28 sec., respectively). As far as the morphology is concerned, we must consider the stimuli as reaching the node at the exact moment of discharge, and hence, following the same distribution pathway. There would be a hindrance to the retrograde conduction of these beats, because the susceptible fibers would be still in their refractory period. At the first reciprocal contraction, the basic rhythm does not change in frequency, and the R-R cycles are constant. During the second recip-

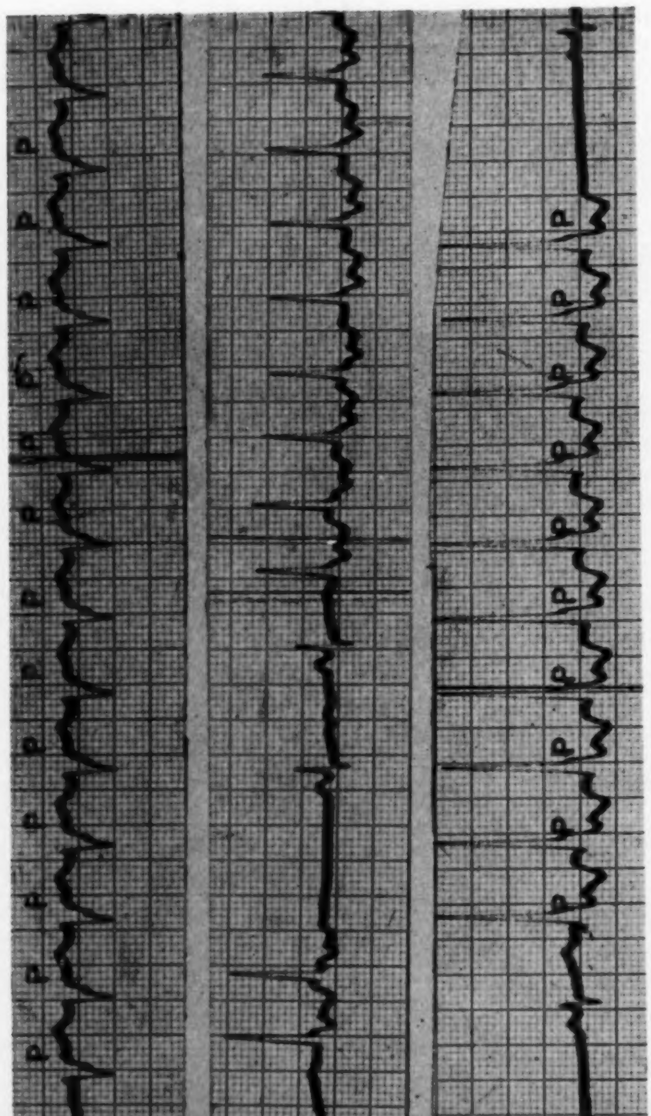


Fig. 2.—Paroxysmal tachycardia of the same origin of the premature beats of Fig. 1.

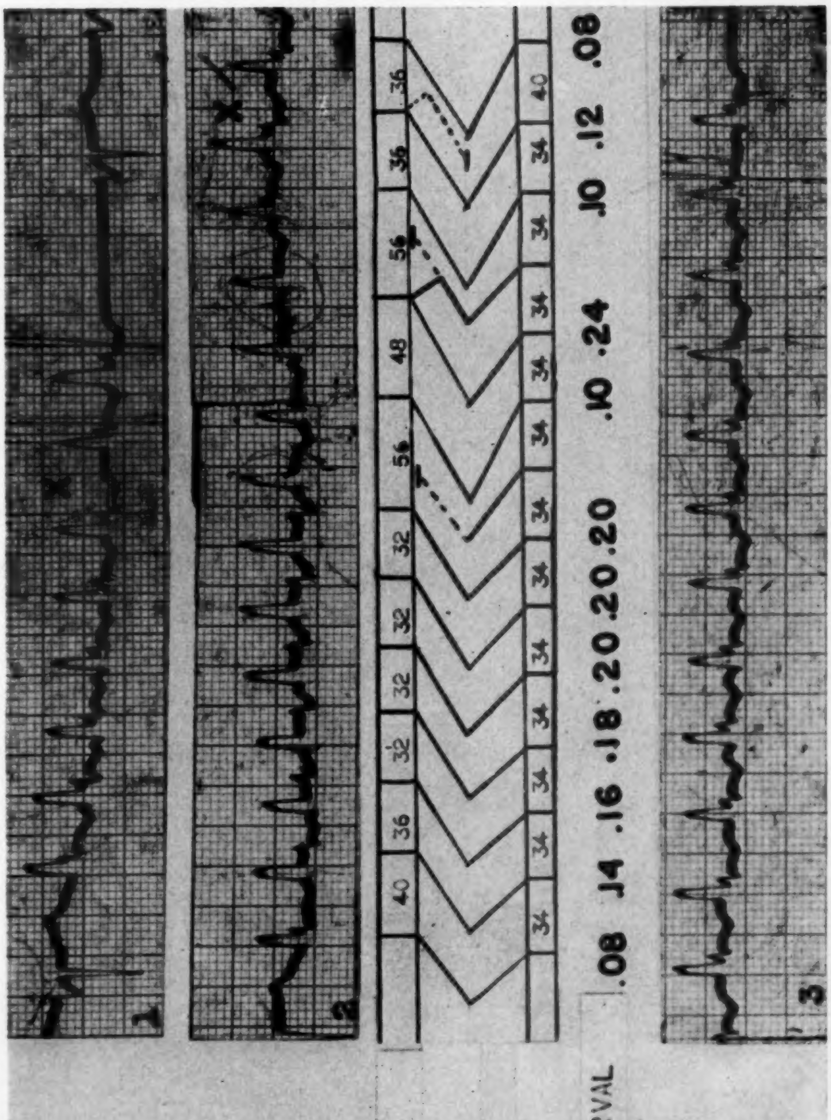


Fig. 3.—Nodal tachycardia with retrograde heart block and aberrant ventricular conduction with a reciprocal beat (fourth ventricular complex from the end of the middle tracing) also conducted aberrantly to the ventricles.

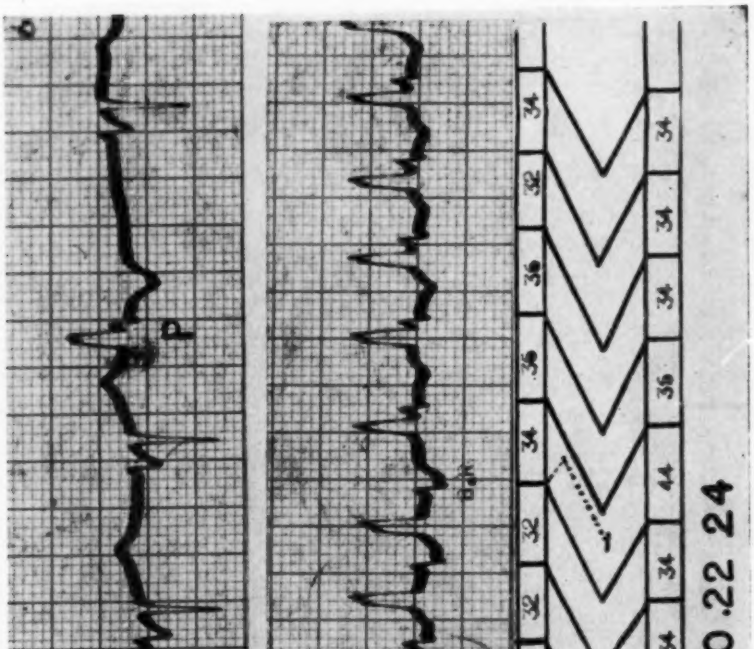


Fig. 4.—Nodal tachycardia with retrograde conduction, blocked re-entry and concealed conduction (lower tracing). An extrasystole of the same focus can be seen in the upper tracing.

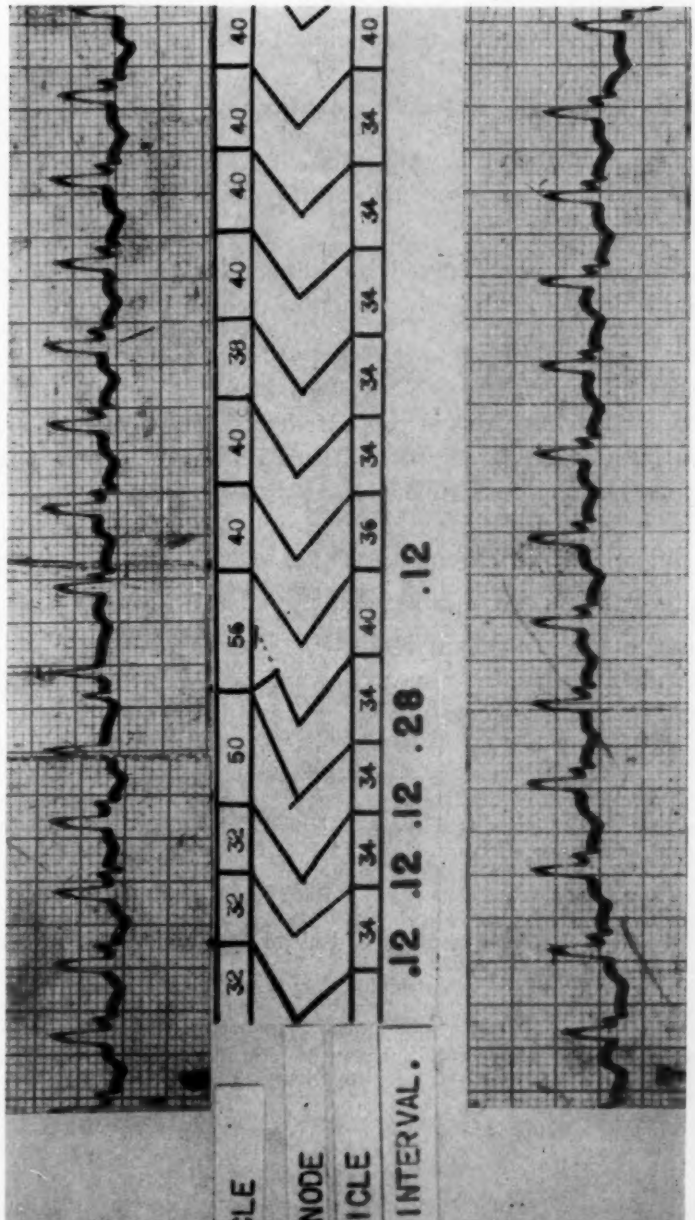


Fig. 5.—Nodal tachycardia with retrograde heart block and reciprocal rhythm (sixth ventricular complex, upper tracing.)

rocal contraction, the next and following nodal complexes change their frequency as much as 0.06 and 0.02 sec., respectively.

We find the most probable explanation is the discharge of the A-V nodal rhythm by a re-entry stimulus with the following delay in the production of a new impulse by the A-V nodal center. This phenomenon would be one of the simplest forms of concealed conduction[6] and can also be seen during blocked reciprocal beats.

Blocked Reciprocal Beats.—R-R cycles of regular frequency (0.34 sec.) are interrupted by lengthened cycles (0.44 and 0.40 sec.), (Fig. 3 upper and middle tracings; Fig. 4, lower tracing). This irregularity could be the result of discharges suffered by the ectopic nodal center and caused by re-entry stimulus; and at the same time the reciprocal beats are blocked at different levels, with no ventricular activity, or response.

Similar cases have been reported by Langendorf, who proposed the term "Concealed conduction" for this phenomenon, which can be observed also in the third case of Bix.[7]

SUMMARY

A case of nodal tachycardia is presented with retrograde heart block, reciprocal rhythm and blocked reciprocal beats, on several occasions displaying the so-called concealed conduction.

SUMMARIO IN INTERLINGUA

Es presentate un caso de tachycardia nodal con retrograde bloco cardiac, rhythmo reciproc, e blocate pulsos reciproc. Esseva observate in illo repetite occurrentias del phenomeno de "conduction celate," i.e., del effecto de blocate impulsos super le formation e conduction del impulso sequente.

REFERENCES

1. Drury, A.: Paroxysmal Tachycardia of A-V Nodal Origin, Exhibiting Retrograde Heart Block and Reciprocal Rhythm, Heart **11**:405, 1924.
2. Langerdorf, R.: Aberrant Ventricular Conduction, Am. Heart J. **41**:700, 1951.
3. Cosh, J. A.: Paroxysmal Nodal Tachycardia With Retrograde Heart Block, Brit. Heart J. **13**:74, 1951.
4. Scherf, D., and Schott, A.: Extrasystoles and Allied Arrhythmias, New York, 1953, Grune & Stratton, Inc., pp. 111-120.
5. White, P. D.: A Study of Atrioventricular Rhythm Following Auricular Flutter, Arch. Int. Med. **16**:517, 1915.
6. Langerdorf, R.: Concealed A-V Conduction: The Effect of Blocked Impulses on the Formation and Conduction of Subsequent Impulse, Am. Heart J. **35**:542, 1948.
7. Bix, H. H.: Various Mechanisms in Reciprocal Rhythm, Am. Heart J. **41**:448, 1951.

SUPRAVALVULAR STENOSING RING OF LEFT ATRIUM IN ASSOCIATION WITH ENDOCARDIAL SCLEROSIS (ENDOCARDIAL FIBROELASTOSIS) AND MITRAL INSUFFICIENCY

H. Milton Rogers, M.D.,* Barzillia R. Waldron, M.D.,* Daniel F. H. Murphey, M.D.,* and Jesse E. Edwards, M.D.**

St. Petersburg, Fla., and Rochester, Minn.

A FIBROUS stenosing ring in the left atrium above the mitral valve in the case to be reported is of interest not only from the point of view of its being a barrier to the escape of blood from the left atrium, but because it seems to be a consequence of earlier and associated insufficiency of the mitral valve. The lesion takes on an added interest from the view that it may be representative of similar lesions for which surgical intervention may be possible in the future. Commissurotomy for mitral stenosis in infants has been reported.[1] It should be pointed out, however, that for the type of lesion under consideration, ablation of an obstructing lesion in the region of the mitral valve might still leave the patient with another in the form of mitral insufficiency.

CASE REPORT

Clinical Features.—The patient, a girl born Sept. 21, 1953, was well until April 6, 1954, when fever and shortness of breath developed and necessitated hospitalization.

The physical examination revealed a well-developed, acutely ill child of 6 months. The temperature was 103° F. by rectum. Râles were heard over the right upper part of the thorax. The heart rate was 160 beats per minute. A systolic murmur, Grade 3, was heard over the precordium and was transmitted to the back. The femoral vessels were easily palpable.

Three blood cultures gave negative results. Studies of the blood disclosed 8.6 grams of hemoglobin per 100 c.c.; 3,050,000 erythrocytes per cu. mm.; and 27,100 leukocytes per cu. mm., with 86 per cent polymorphonuclear leukocytes, and 14 per cent lymphocytes.

With oxygen and antibiotic therapy convalescence was uneventful. The patient was dismissed from the hospital in 6 days. She remained well until May 9, 1954, when slight cough, fever, and shortness of breath developed. She was readmitted to Mercy Hospital, St. Petersburg, on May 9, 1954, because of cyanosis, dyspnea, and fever of 101° F. by rectum. There was no thrill, and the systolic murmur previously noted was not audible. The cardiac rate was 160 beats per minute. The pulmonic second sound was greater than the aortic second sound. Treatment with antibiotics, digitalis, and oxygen was initiated.

The roentgenogram of the thorax revealed marked cardiac enlargement (Fig. 1). The heart was globular. There was uplifting of the apex. Evidence of congestion was present in both lungs. The electrocardiogram revealed sinus rhythm with a rate of 180 beats per minute. The electrical axis was plus 100 degrees (Fig. 2). There was no significant change in the S-T segment. The T waves were inverted in precordial Leads V_1 through V_4. The R wave was greater than the S wave in Leads V_1 through V_6. The findings were consistent with those of right ventricular hypertrophy.

Received for publication Feb. 28, 1955.
*Mercy Hospital, St. Petersburg, Fla.
**Section of Pathologic Anatomy, Mayo Clinic, Rochester, Minn.

The patient showed temporary improvement for several days, and then heart failure increased. Death occurred on May 26, 1954, at the age of 8 months.

Pathologic Findings.—At necropsy the pertinent findings were confined to the heart and lungs. The most striking change was evident in the vicinity of the mitral valve. Just above the base of the valve and encircling the left atrium above the valve was a ring of fibrous tissue which

Fig. 1.—The thorax at time of second admission to the hospital.

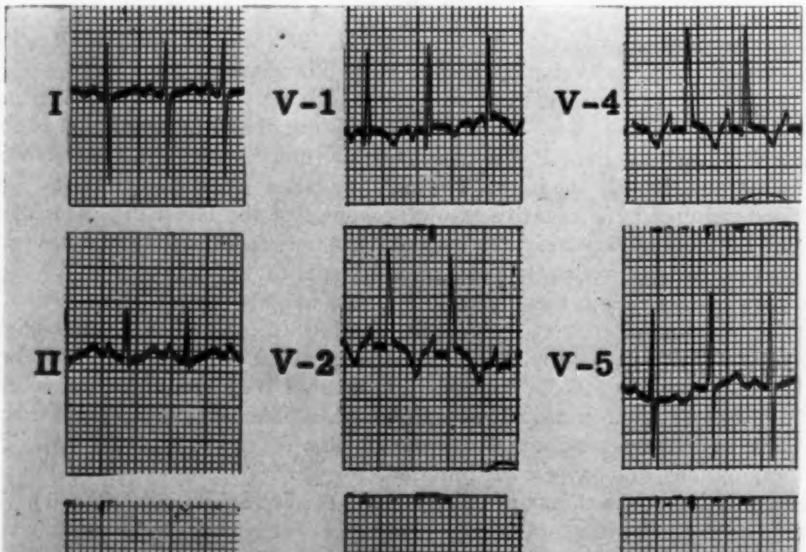


Fig. 2 —Electrocardiogram.

protruded for 3 mm. into the left atrial cavity (Fig. 3). The ring of fibrous tissue in effect acted as a stenosing membrane just above the mitral orifice. The diameter of the left atrium at the level of the supravalvular membrane was about 6 mm. The left ventricle was of normal size. In the region of the left posteromedial papillary muscles, there was endocardial thickening of moderate degree. The mitral chordae were shorter than normal. The valve leaflets themselves were not remarkable, but the posterior leaflet seemed to have been restrained by the short chordae. The left atrium was dilated, and its walls showed thick muscle and thickened endocardium.

The wall of the left ventricle measured 6 mm. in thickness. The right ventricle was hypertrophied and the chamber dilated. Its wall also measured 6 mm. in thickness. The tricuspid and pulmonary valves were normal. The aortic valve was congenitally bicuspid with a raphe running from the aortic wall onto the conjoined leaflet. The two coronary arteries arose above the con-

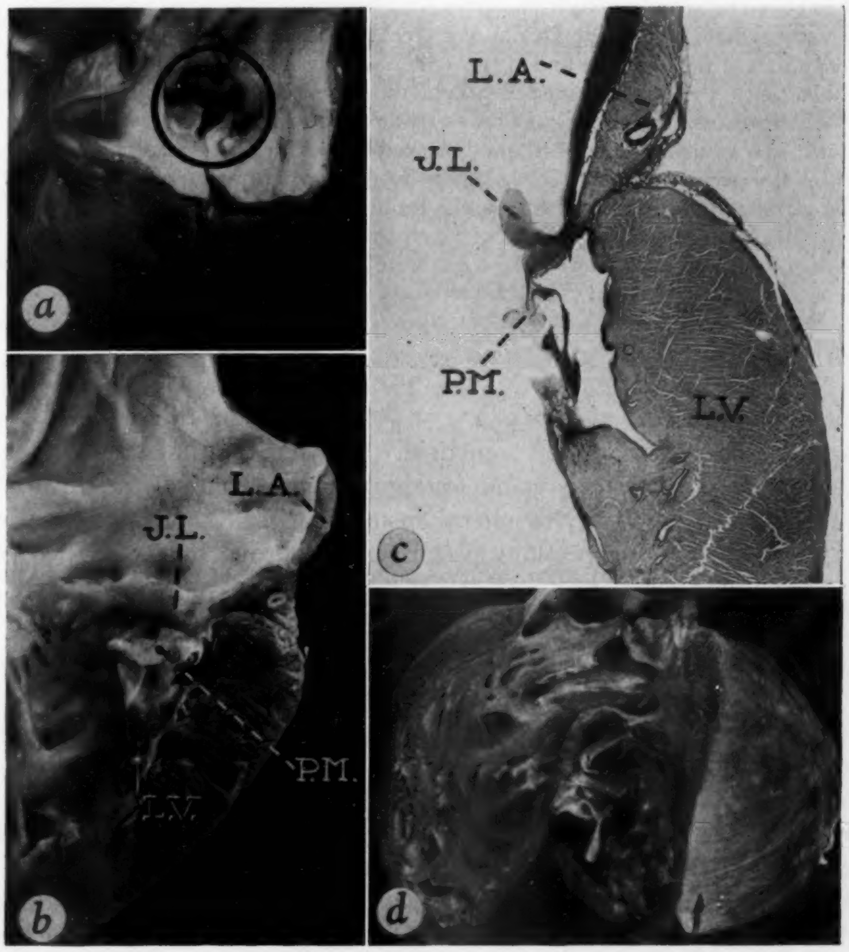


Fig. 3.—*a*, Interior of left atrium from above showing the stenosing membrane (within circle) which lies above the mitral valve and obscures it from view. Thickening of the endocardium of the left atrium was present. *b*, A portion of the left atrium (*L.A.*) and ventricle (*L.V.*), and the posterior leaflet of the mitral valve. Short chordae associated with endocardial thickening. Insertion of papillary muscle is almost directly into the posterior mitral leaflet (*P.M.*); above the leaflet a ridge of tissue projecting into the lumen (*J.L.*) represents the stenosing supravalvular ring seen in *a*. *c*, Section through posterior mitral leaflet and adjacent portions of the left atrium and ventricle. Abbreviations as in *b*. Short chordae associated with some endocardial thickening in the left ventricle. Above the posterior mitral leaflet is the ridge of tissue representing the stenosing membrane seen in *a*. (Verhoeff's elastic-tissue stain counterstained with van Gieson's elastic-tissue stain; ×3.5). *d*, Dilatation and hypertrophy of right ventricle.

joined leaflet. The foramen ovale was anatomically sealed. There was no ventricular septal defect. The ductus arteriosus was closed.

Gross examination of the lungs revealed edema. In addition a prominent gray network was apparent in the visceral pleura.

Microscopic examination of the mitral valve and adjacent portions of the left ventricle and left atrium revealed several changes. At the ventricular insertion of the chordae from the posterior leaflet there was localized thickening of the left ventricular endocardium by connective tissue containing elastic tissue. Elsewhere the endocardium of the left ventricle showed focal thickening with elastic tissue, whereas many parts showed no particular change. The leaflets of the mitral valve itself did not appear remarkable, but along their atrial surfaces at their bases there was localized thickening by connective tissue heavy in elastic content. This localized thickening protruded into the cavity of the heart and corresponded with the membrane which was noted above the mitral orifice in the gross examination.

The endocardium of the left atrium was greatly thickened by collagen and elastic tissue. The myocardium of the ventricle and of the atrium was normal.

Examination of the lungs revealed edema and the presence of varying numbers of macrophages in the alveolar spaces. Small foci of fibrous tissue in the alveolar spaces suggested organized pneumonia. The pulmonary vessels showed marked thickening of the medial layer of the muscular arteries both large and small. In the arterioles there was some intimal fibrous proliferation. The walls of veins were thickened by fibrous intimal proliferation and by enlargement of the media, resulting mainly from deposition of much collagen and elastic tissue in this layer. The lymphatics of the pleura and interlobular septa were relatively wide. These seemed to represent the gray network seen grossly in the pleura.

COMMENT

Our interpretation of the primary disturbance in this case is congenital endocardial sclerosis of the left ventricle. The endocardial lesions, though not widely distributed, were responsible for shortening of some of the mitral chordae. This shortening in turn led to mitral insufficiency. The systolic murmur observed during the first hospital admission supports this conclusion.

The stenosing ring above the mitral value is of considerable interest and is unusual. We are of the opinion that it represents a reaction to the trauma of regurgitant streams of the blood and in this way may be termed a "jet lesion" or a "regurgitant lesion." In mitral insufficiency, jet lesions may be readily observed in the left atrium, but they do not usually take the form encountered in this case. Usually they are represented by a localized area of endocardium in the left atrium that is irregularly thickened by foci of fibrous tissue in little cusplike formations. The peculiar site of the jet lesion in our case is interpreted by us as the result of peculiar directions to the regurgitant streams. It is possible that the lesion was more localized at earlier periods. As some of the lesion was formed, it was responsible for deflecting the regurgitant streams in new directions, thus setting the stage for completion of the ringlike lesion.

One of us (J.E.E.) has observed a similar formation above the left atrioventricular valve in a 3-year-old patient with corrected transposition of the great vessels and insufficiency of the left atrioventricular valve. Case 2 in the paper of Kipkie and Johnson[2] is concerned with an 11-year-old boy with the Eisenmenger complex, and with necrotizing changes in the pulmonary vessels. A narrow band of connective tissue 1 to 2 mm. in width and 1 mm. in thickness running circumferentially above the mitral valve was noted. Beyond

this no details were given by Kipkie and Johnson, but the band or ring described by them bears resemblance to the ring described in this paper.

If our interpretation is correct, the stenosing ring above the mitral valve is to be viewed as an acquired lesion secondary to a congenital malformation (endocardial sclerosis with mitral insufficiency).

The stenosing ring above the mitral valve may be viewed as dividing the left atrium into two chambers, however small the lower. This concept introduces the subject of cor triatriatum since in that condition the left atrium is also represented by two chambers. In cor triatriatum, however, the two chambers are of about equal size and the upper receives the pulmonary veins and communicates with the lower chamber through an opening of varying size. The lower chamber communicates with the left auricular appendage and with the mitral valve. In the case here reported the pulmonary veins entered the same chamber which communicated with the left auricular appendage and the condition, cor triatriatum, does not seem applicable.

The pulmonary edema, vascular changes, the dilatation and hypertrophy of the left atrium, and the right ventricular hypertrophy may all be viewed as consequences of the mitral insufficiency and of the obstruction caused by the supravalvular ring. In other cases of this type an operation for the relief of mitral stenosis might be planned. The case reported emphasizes the point that the functional disturbances at the mitral region were complicated. Were the stenosis imparted by the supravalvular ring overcome surgically, the problem of the associated and underlying mitral insufficiency would remain as a challenge in therapy.

SUMMARY

Reported is the case of an infant dying of heart failure at the age of 8 months with evidence of mitral valvular disease. Necropsy revealed a stenosing membrane above the mitral valve. This is interpreted as being an acquired "jet lesion" which resulted from mitral insufficiency accompanying congenital endocardial sclerosis of the left ventricle.

SUMMARIO IN INTERLINGUA

Es reportate le caso de un infante qui moriva de dysfunctionamento cardiac al etate de 8 menses con signos de morbo mitrovalvular. Le necropsia revelava supra le valvula mitral le presentia de un membrana anular a effecto stenotic. Nos opina que illo representa un reaction al trauma de regurgitante fluxos de sanguine. De accordo con isto nos lo designa como un "lession regurgitante." In le caso presente le lesion regurgitante es interpretate como un lesion acquirite in consequentia de insufficientia mitral accompaniante congenite sclerosis endocardial del ventriculo sinistre.

REFERENCES

1. Maxwell, G. M., and Young, W. P.: Isolated Mitral Stenosis in an Infant of Three Months: Report of a Case Treated Surgically, AM. HEART J. **48**:787, 1954.
2. Kipkie, G. F., and Johnson, D. S.: Possible Pathogenic Mechanisms Responsible for Human Periarteritis Nodosa, as Suggested by the Occurrence of Two Instances of This Disease in Association With Glomerulonephritis, Arch. Path. **51**:387, 1951.

Review

NEOPLASTIC DISEASE OF THE HEART

J. WILLIS HURST, LIEUTENANT COMMANDER, (MC) USNR,* AND
HENRY R. COOPER, COMMANDER, (MC) USN

BETHESDA, MD.

NEOPLASTIC disease of the heart is overlooked with great regularity even though it is no longer considered unusual. This type of disease is usually difficult to recognize but can occasionally be identified if the physician considers the possibility along with certain diagnostic clues.

The purpose of this report is to point out the cardiac manifestations of neoplastic disease. The material presented here is developed entirely from the clinical viewpoint and is designed to aid the clinician in his diagnostic endeavors. The details of the pathologic picture have been omitted. The diagnostic clues were formulated after studying our own cases and reviewing the abundant literature on the subject. Three cases are presented to illustrate various clinical points of interest.

Although little can be done for this type of disease our futility is not sufficient reason to ignore its existence, for medical therapy is always better directed when all the ramifications of a disease are understood. Some benign tumors of the heart can be removed, and roentgen therapy may occasionally be transiently beneficial in some cases. Moreover, certain surgical procedures, while not curative, may relieve agonizing symptoms.

CASE REPORTS

The following cases have been selected because they illustrate a large number of diagnostic clues and, therefore, serve as a background for the discussion which follows.

CASE 1.—A 79-year-old Negro was first admitted to the United States Naval Hospital in Bethesda, Maryland, on May 26, 1954, with a 3-month history of a gradually enlarging superficial chest mass. Examination disclosed an orange-size subcutaneous tumor overlying the third right sternocostal junction. The mass was firm and not tender. Bilateral lymphadenopathy and left pleural effusion were also present. Urinary tract obstruction due to enlargement of the prostrate was present. The blood pressure was 170/80 mm. Hg, and examination of the heart was normal. Laboratory studies revealed a marked anemia and a leukemoid reaction. An electrocardiogram was normal. A large pleural effusion was noted on the chest x-ray. A diag-

---

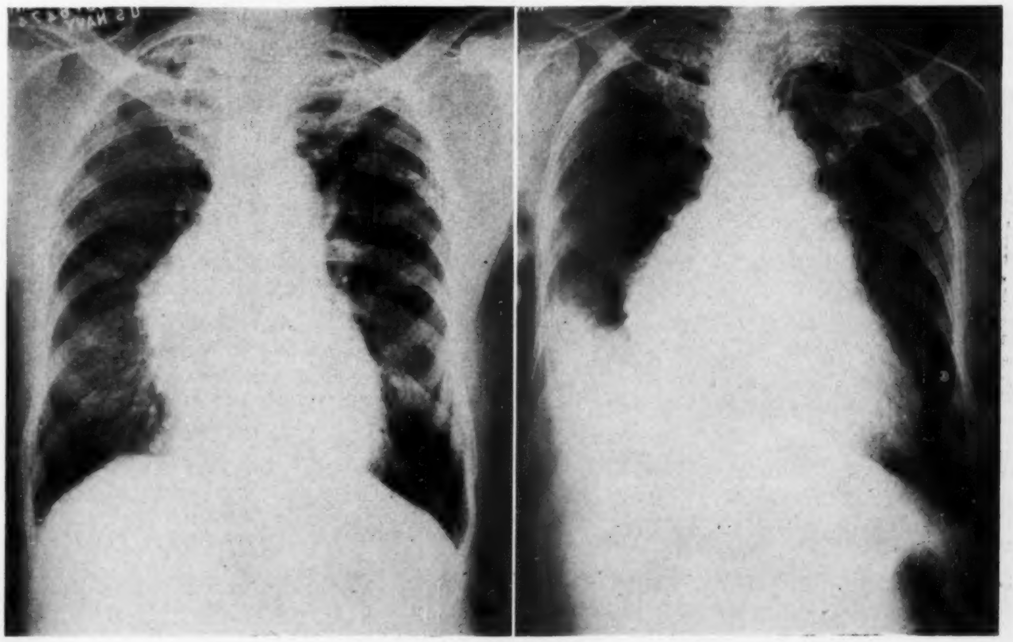
From the Cardiology Section of the Department of Medicine, United States Naval Hospital, Bethesda, Md.

Received for publication May 7, 1955.

*Associate Cardiologist, Emory University Hospital, Atlanta, Ga.; on leave of absence to serve in the United States Navy.

nosis of reticulum cell lymphosarcoma was made by axillary node biopsy. Treatment with cortisone, blood transfusions, and Foley catheter drainage resulted in asymptomatic ambulation, decrease in the size of the chest tumor, and discharge from the hospital on Aug. 4, 1954.

The patient was readmitted to the hospital on Oct. 18, 1954, with urinary tract obstruction. The chest tumor then measured 5 × 7 cm. Examination of the heart was again normal. The electrocardiogram and chest x-ray were normal. X-ray of the chest on Oct. 19, 1954, revealed a right inferior hilar mass contiguous with the right heart border (Fig. 1,*A*). On Nov. 17, 1954, a transurethral resection was performed. On Dec. 2, 1954, the patient suddenly developed acute pleuritic pain suggesting pulmonary infarction. During the next five days severe dyspnea, cardiac enlargement, distended neck veins, hepatomegaly, a ventricular gallop, atrial fibrillation with an uncontrolled ventricular rate of 200, and pulsus paradoxus developed. There was marked bronchial breathing over the lower end of the sternum which was believed to be due to neoplastic involvement of the anterior mediastinal structures extending from the trachea and bronchi to the sternum. On Dec. 13, 1954, x-ray of the chest revealed right hydrothorax and a markedly



A. *B.*

Fig. 1.—Chest x-rays of a patient with reticulum cell lymphosarcoma. *A*, X-ray of the chest made on Oct. 19, 1954, showing a right hilar mass contiguous with the right border of the heart and bilateral tuberculosis. *B*, X-ray of the chest made on Dec. 13, 1954, showing marked cardiac enlargement, a "lumpy" right-heart border, and right hydrothorax.

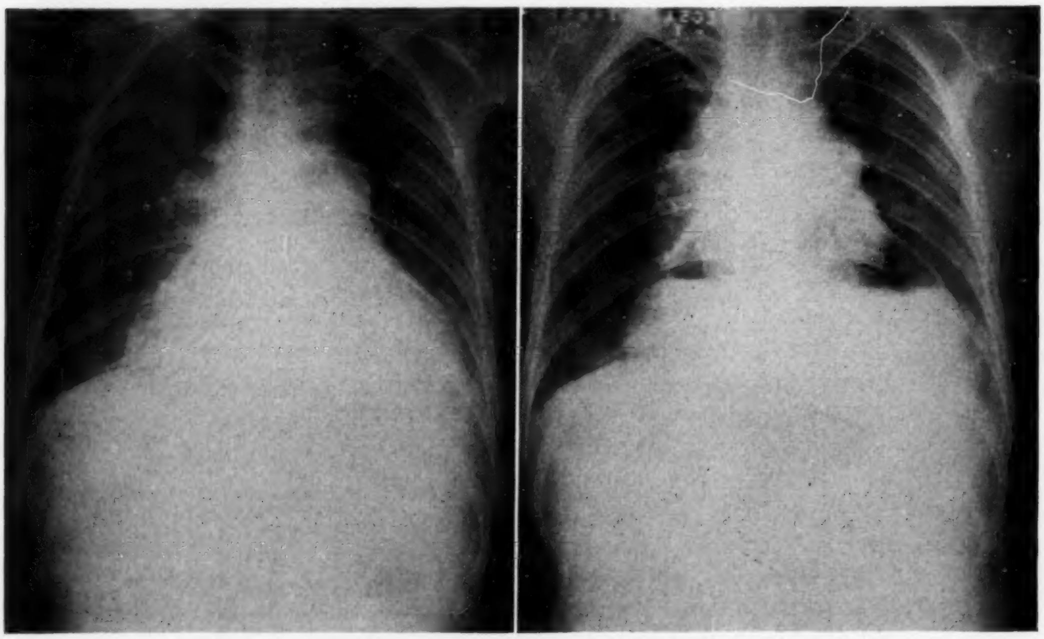
enlarged heart (Fig. 1,*B*). The electrocardiogram was consistent with septal infarction and pericarditis. Bloody fluid, 200 c.c., was aspirated from the pericardial space. The cardiac complications in this case were believed to be due to malignant invasion of the pericardium and myocardium. In addition, superior vena caval obstruction was suspected. The cardiac rhythm reverted to normal after digitalization. The superficial chest mass disappeared, and the heart size decreased after x-ray therapy. The patient improved considerably but suddenly expired on Dec. 28, 1954.

At autopsy no superficial chest mass could be found. Both pleural cavities were obliterated by neoplastic tissue. The myocardium was completely replaced by tumor tissue for a distance of 5 to 8 mm., and the pericardial cavity was filled with similar tissue. The endocardium was not involved, and the coronary arteries showed only minimal atherosclerosis. On microscopic

examination neoplastic cells, characteristic of reticulum cell lymphosarcoma, were found infiltrating and replacing cardiac muscle fibers.

This patient illustrates several features of neoplastic disease of the heart. He developed congestive heart failure, cardiac enlargement, auricular fibrillation, and electrocardiographic evidence of pericarditis and myocardial infarction. The unusual physical finding of bronchial breathing over the lower sternum due to tumor tissue was noted. The true cause of his heart disease was suspected because the common causes of heart disease could be eliminated and because he exhibited a superficial chest mass which was known to be a reticulum cell lymphosarcoma. The x-ray finding of a right inferior hilar mass contiguous with the right heart border supported the impression that there was neoplastic involvement of the heart and pericardium.

CASE 2.—A 32-year-old white female was admitted to the United States Naval Hospital in Bethesda, Maryland, on Nov. 12, 1954, with a 4-month history of progressive dyspnea, "asthma," coughing episodes, and a 10-pound weight loss. Examination revealed a temperature of 101° F., and a pulse rate of 110 beats per minute. The superficial neck veins were only slightly distended, but a prominent deep systolic jugular pulse wave was noted. Ewart's sign was present, and small left supraclavicular lymph nodes were noted. X-ray of the chest disclosed an enlarged cardiac silhouette and enlarged hilar lymph nodes. An electrocardiogram showed low voltage.



A. *B.*

Fig. 2.—Chest x-rays of a patient with massive hemorrhagic pericardial effusion secondary to bronchogenic carcinoma. *A*, X-ray of the chest made on Dec. 13, 1954, showing a large cardiac silhouette, clear lung fields, and bilateral hilar lymphadenopathy. (Cardiac fluoroscopy revealed greatly diminished cardiac pulsations.) *B*, X-ray of the chest made after the removal of 1,200 cubic centimeters of bloody fluid.

The patient had received cortisone for asthma prior to admission and the reliability of the negative tuberculin skin test was questioned. The laboratory studies indicated a hypochromic anemia and slight leukocytosis with a normal differential. The initial clinical impression was lymphoma with pericardial and myocardial involvement, but supraclavicular lymph node biopsy was inconclusive and x-ray therapy produced no response. Dyspnea and orthopnea progressed and clubbing of the fingers developed. The cardiac silhouette increased in size, and the cardiac pulsations decreased while the lung fields remained clear. A pulsus paradoxus then appeared

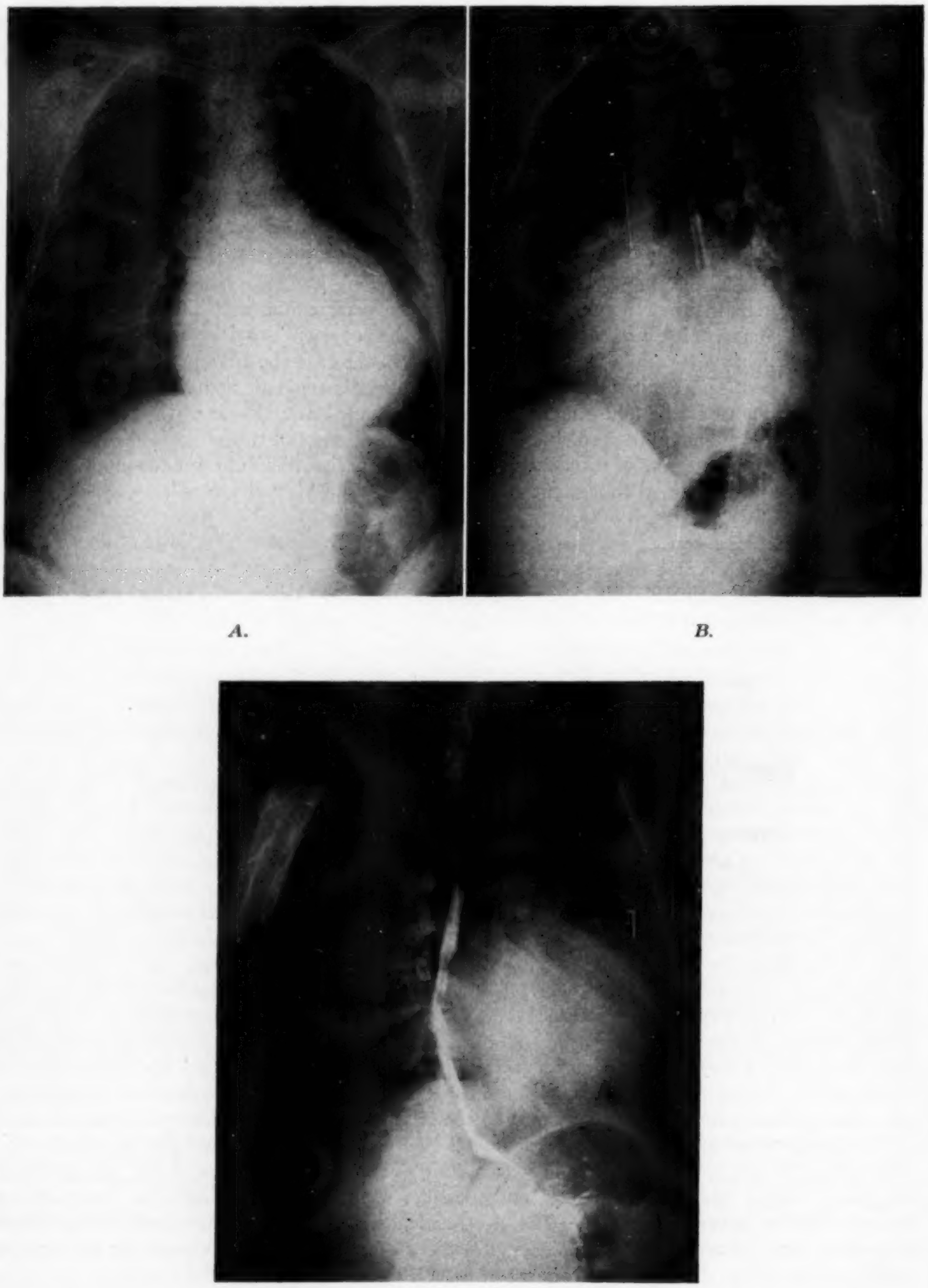
indicating progressive cardiac tamponade. Four pericardial taps were performed each of which yielded from 700 to 1,200 c.c. of bloody fluid. The pericardial fluid contained malignant cells but the type of neoplasm could not be determined. After the third and fourth pericardial aspirations radioactive chrome phosphate was instilled into the pericardial sac. Plans had been made to perform a pericardial resection or to produce a pleuropericardial window since it was obvious that the fluid collected in the pericardial space with great rapidity and the radioactive chrome phosphate was not effective. X-ray of the chest on Dec. 13, 1954, showed a huge pericardial effusion (Fig. 2, *A*, *B*). Unfortunately, the patient developed acute dyspnea and cardiac standstill, one hour after a pericardial tap, on Dec. 13, 1954. Emergency thoracotomy and cardiac massage restored the cardiac rhythm and respiration; however, the patient failed to regain consciousness and expired 7½ hours after thoracotomy.

At autopsy small tumor nodules were seen on the pericardium and the epicardial surface of the heart. Microscopic examination disclosed that the neoplasm was a bronchogenic carcinoma and that the primary site was in the carina. As is often the case the amount of pericardial fluid that had developed seemed out of proportion to the number of neoplastic nodules found.

This case illustrates the following characteristics of neoplastic disease of the heart and pericardium. The development of cardiac tamponade in the absence of tuberculosis or other obvious cause was strongly suggestive of neoplastic disease. The pericardial fluid was bloody, reaccumulated rapidly, and contained malignant cells thereby establishing the neoplastic origin of the disease. The initial diagnosis was lymphoma; however, this diagnosis was doubted when the tumor failed to respond to x-ray therapy. This case also indicates that the long half-life isotopes, such as radioactive chrome phosphate, are inadequate in the treatment of neoplastic disease of this type since the pericardial fluid accumulated too rapidly. Pericardial resection or the production of a pleuropericardial window appears to be the treatment of choice.

CASE 3.—A 42-year-old white female nurse was first seen in the Cardiac Department of the United States Naval Hospital at Bethesda, Maryland, on Oct. 5, 1954, complaining of dyspnea on effort and paroxysmal rapid heart action. She gave the following past history. In October, 1951, she experienced a 24-hour period of retrosternal pressure and slight temperature elevation. The chest x-ray and electrocardiogram were normal. On March 7, 1953, she developed the signs and symptoms of acute pericarditis including substernal pain aggravated by breathing, dyspnea, slight temperature elevation, leukocytosis, pericardial friction rub, typical electrocardiographic findings, and enlargement of the cardiac silhouette. After the pericardial friction rub disappeared, a Grade 2 apical systolic murmur developed. After a decrease in heart size, concurrent with clinical improvement, the heart slowly enlarged and thereafter the x-ray of the chest was characterized by a 13-millimeter area of radiolucency covering the entire left ventricle. Because the diagnosis was not clear, a pericardial biopsy was performed in April, 1954. At the time of the operation adhesive pericarditis was found at the cardiac apex, and the biopsy was reported to show nonspecific fibrous pericarditis. On Oct. 5, 1954, examination disclosed normal blood pressure, a very forceful cardiac pulsation in the third, fourth, and fifth left intercostal spaces about 4 to 6 cm. from the sternum. There was a Grade 3 systolic murmur at the apex, and a loud third sound was heard in early diastole at the apex suggesting the opening snap of the mitral valve, but no diastolic murmur was heard. The hepatojugular reflex was positive, and there was moderate hepatomegaly. X-ray of the chest on Oct. 4, 1954, disclosed clear lung fields and a 13-millimeter area of radiolucency over the left lower heart border in the posteroanterior view (Fig. 3, *A*,*B*,*C*). On fluoroscopic examination of the heart, the "area of the left ventricle" was large, bulged posteriorly, and did not pulsate. The left atrium was large, irregular, and located slightly higher than usual. The electrocardiogram was compatible with left atrial enlargement and epicardial ischemia. Hematologic studies were normal except for an elevated sedimentation rate.

The unusual features of the case included the unusual location of the cardiac pulsation on physical examination, the loud apical systolic murmur, and "opening snap of the mitral valve" associated with a large but nonpulsating "left ventricle." It was reasoned that the left ventricle should pulsate if the enlargement was due to rheumatic heart disease. Because of the atypical features of the case, cardiac catheterization was performed. The study revealed normal pulmonary artery and right ventricular pressures. The right ventricular pressure curve was not charac-



A. B.

C.

Fig. 3.—Chest x-rays of a patient with neuroblastoma of the mediastinum. *A*, Posteroanterior view of the chest showing a large cardiac silhouette. In addition, there is an area of radiolucency adjacent to the left cardiac border. *B*, Left anterior oblique view showing enlargement of the "left ventricular region" of the heart. (Cardiac fluoroscopy revealed no pulsation of the "left ventricular region.") *C*, Right anterior oblique view showing an irregularly indented esophagus in the region of the left atrium.

teristic of the wave form said to occur in constrictive pericarditis. Biplane angiocardiograms were made at the National Heart Institute in Bethesda, Maryland, by Dr. Robert Grant and indicated that there was a large mass located posterior to the heart (Fig. 4). The mass forced the left ventricle forward and also compressed the left and right atrium. A clay model of the tumor and the distorted cardiac chambers was fashioned by Dr. Robert Grant, after studying the angiocardiograms (Fig. 5,*A*,*B*,*C*,*D*). On Nov. 10, 1954, the patient was operated on by

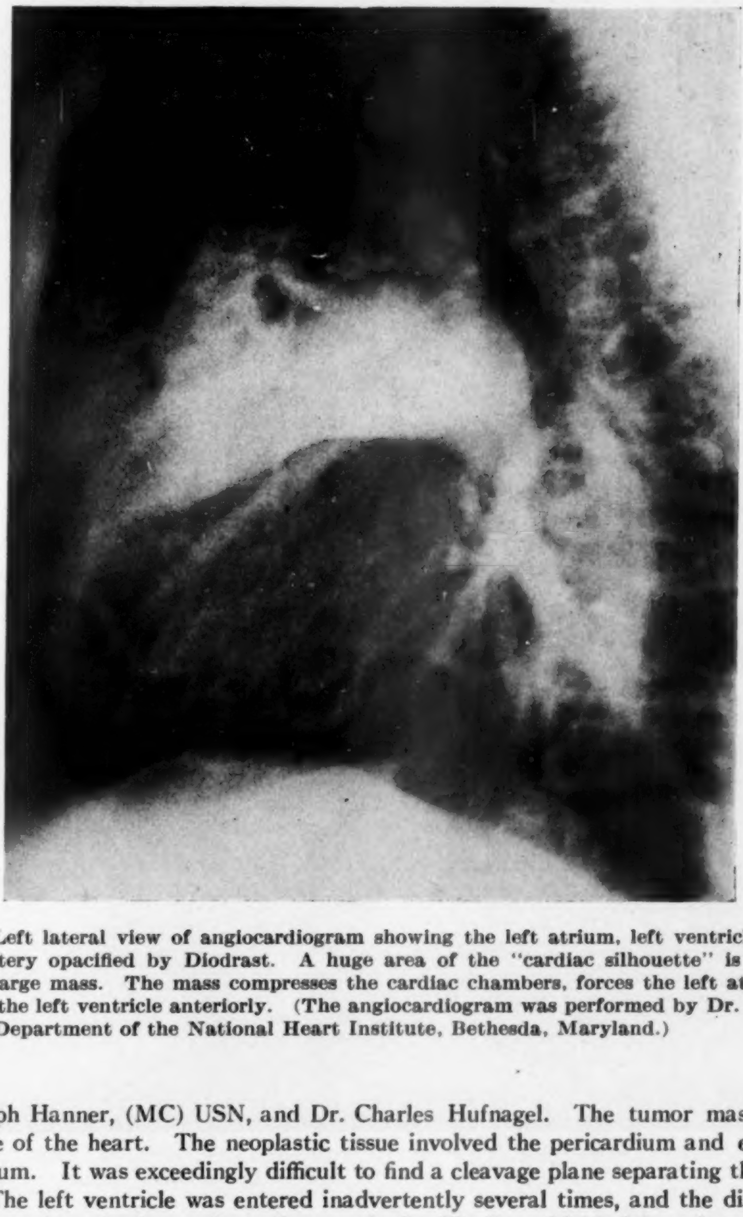


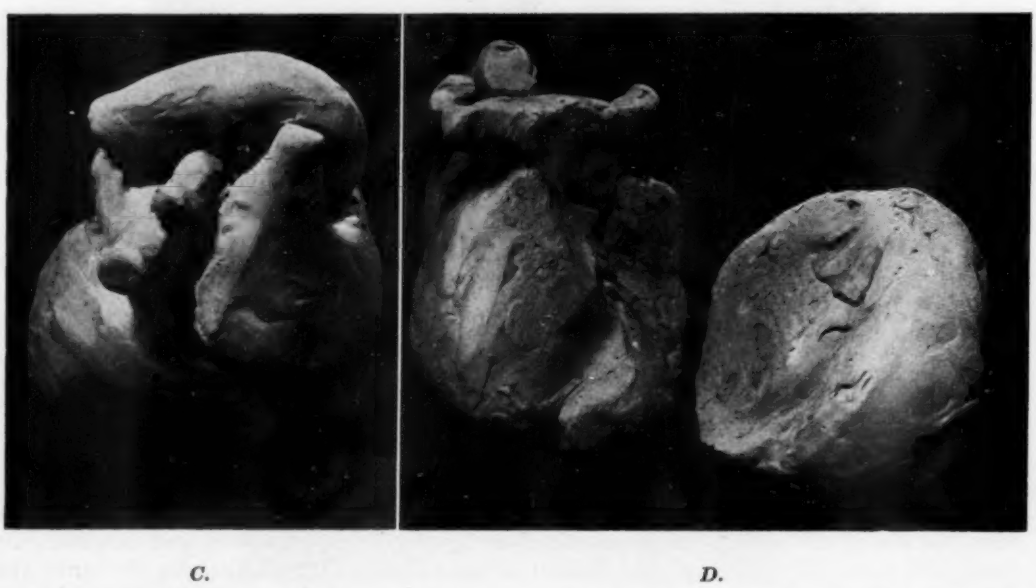
Fig. 4.—Left lateral view of angiocardiogram showing the left atrium, left ventricle, aorta, and pulmonary artery opacified by Diodrast. A huge area of the "cardiac silhouette" is not opacified because of a large mass. The mass compresses the cardiac chambers, forces the left atrium upward, and displaces the left ventricle anteriorly. (The angiocardiogram was performed by Dr. Robert Grant in the X-ray Department of the National Heart Institute, Bethesda, Maryland.)

Captain Joseph Hanner, (MC) USN, and Dr. Charles Hufnagel. The tumor mass was about twice the size of the heart. The neoplastic tissue involved the pericardium and extended into the myocardium. It was exceedingly difficult to find a cleavage plane separating the tumor and the heart. The left ventricle was entered inadvertently several times, and the distorted heart could not respond to the hemorrhage that resulted. Finally a friable left atrium was entered, and effective cardiac function soon ceased.

At autopsy a large tumor mass measuring 16 × 12 × 9 cm. was found partially removed from the heart (Fig. 6). The mass compressed the left ventricle and projected into the left and right atrial cavities. There were metastatic lesions in the mediastinal lymph nodes.

The microscopic sections of the tumor were shown to many pathologists. All agreed that the neoplasm was malignant, but no uniform agreement was reached regarding the true nature of the tissue. After considering all possibilities the final diagnosis was neuroblastoma of the pericardium.

A. *B.*



C. *D.*

Fig. 5.—Clay model of the heart and tumor constructed after studying the angiocardiograms. *A*, Posteroanterior view showing the mass extending beyond the left heart border. *B*, Left lateral view showing the mass posteriorly. The left atrium and ventricle are distorted. *C*, Right lateral view showing the mass adjacent to the right atrium. *D*, The tumor has been separated from the heart. The mass appears to be as large as the heart. The posterior portion of the heart, including the right atrium, left atrium, and ventricle were compressed by the mass. (The clay model was fashioned by Dr. Robert Grant at the National Heart Institute in Bethesda, Maryland.)

This case illustrates the following points. The patient gave a history of pericarditis and paroxysmal rapid heart beat. The loud systolic apical murmur and "opening snap of the mitral valve" only superficially suggested rheumatic heart disease since the "left ventricle" was large but did not pulsate. The left atrium was irregular and was located slightly higher than usual. The diagnosis was established by angiocardiography. This case also indicates that pericardial biopsy does not always reveal the true nature of the pericardial disease.

Fig. 6.—Photograph of the tumor mass (neuroblastoma) found adjacent to the heart in Case 3.

DISCUSSION

Incidence.—Earlier literature indicated that cardiac metastases occurred in only a small per cent of patients dying of malignancy.[1-3] The recent studies of three independent groups of workers indicate that such lesions of the heart are relatively common in patients with neoplastic disease.[4-6] These three groups of investigators carefully studied a total of 1,264 patients dying of malignancy and found cardiac lesions at autopsy in approximately 20 per cent. This apparent increase in frequency in cardiac metastatic lesions during the last thirty years is due to two factors. There has been an increasing amount of interest in the subject and, in addition, patients with neoplastic disease are now living longer because of better supportive medical care, thereby allowing more time for metastases to occur.

Although the heart is involved in 20 per cent of patients dying of malignancy, there are several neoplastic processes that can be implicated with even greater regularity not only because of their tendency to involve the heart, but also because they are among the common malignancies. For example, carcinoma of

the breast and of the bronchus are common neoplasms, and metastases to the heart and pericardium occur in one out of three cases. The heart and pericardium are involved in one out of two patients with leukemia. These structures are involved in one out of six patients with lymphoma. Malignant melanoma, a much rarer neoplasm than those just listed, is important to this discussion because metastases to the heart and pericardium occur in over 50 per cent of the cases. Carcinoma of the kidney, of the esophagus, of the testis, of the naso-oropharynx, and of the pancreas frequently metastasizes to the heart and pericardium while carcinoma of the stomach, though common, rarely metastasizes to these structures.

A neoplastic process can spread to the heart and pericardium by the blood stream, by the lymphatics, and by direct invasion. When metastatic lesions are found in the heart and pericardium, lesions are usually found in other viscera, especially the lungs, when they are carefully studied at autopsy. Any part, or all parts, of the heart may be involved with neoplastic tissue. In patients with leukemia the heart is frequently diffusely infiltrated.[4] Recent data favor the concept that all parts of the heart are equally susceptible to metastatic lesions and that different parts are affected in direct proportion to their bulk.[7] Metastatic lesions are more likely to be found in the pericardium and myocardium and are found infrequently in the endocardial region.

Most metastatic lesions of the heart produce no signs or symptoms, and the cardiac involvement is not recognized during life. Such lesions may be unimportant in the over-all clinical picture but may, under certain circumstances, produce considerable discomfort and contribute to the death of the patient. It is the authors' view that metastatic cardiac disease can be identified in perhaps 5 to 10 per cent of patients dying of neoplastic disease.

Metastatic cardiac involvement must always be considered when a patient with known malignancy develops signs and symptoms referable to the heart. Such consideration is especially important when the usual causes of heart disease can be eliminated. The clinical manifestations of metastatic neoplastic involvement of the heart will be discussed subsequently.

Primary neoplasms of the heart are exceedingly rare. The types of tumors likely to be encountered will be indicated in the discussion that follows. Although rare, primary neoplasms of the heart must always be considered in the differential diagnosis of unusual heart disease. It is even more vital to recall this possibility when dealing with certain clinical syndromes. For example, a myxoma is the most common primary tumor of the heart, and it frequently simulates mitral stenosis.

Clinical Manifestations.—Primary and secondary neoplasms of the heart may involve the endocardium, the myocardium, and the pericardium. From a practical clinical standpoint one can think in terms of (1) a clinical picture due to a neoplastic involvement of the endocardial region, (2) a clinical picture due to neoplastic involvement of the myocardial region, and (3) a clinical picture due to neoplastic involvement of the pericardium. This type of classification will be worthless to the pathologist but has some merit for the clinician since it

enables him to predict the symptoms which might occur when a tumor is located in a certain part of the heart. Such an approach may reveal the first clue to the diagnosis but may not be helpful in identifying the exact type of neoplasm since many neoplasms may produce similar symptoms and signs. Actually all regions of the heart may be involved simultaneously or a neoplasm may originate in one region of the heart and be asymptomatic producing symptoms only by invading adjacent tissue. Accordingly, one cannot assume that the clinical picture characteristic of the involvement of a certain region necessarily indicates that the neoplasm actually arose in that region.

Cardiac arrhythmias may be associated with neoplastic disease of the heart and are discussed separately. The electrocardiographic and x-ray findings, including angiocardiography, are also discussed.

1. *Neoplastic involvement of the endocardial region:* Neoplastic metastatic tissue may be implanted on the heart valves, mural endocardium, chordae tendineae, and papillary muscles. Such lesions are rare and seldom produce symptoms and signs of heart disease. Degenerative verrucal endocardial lesions may occur during the course of a large variety of diseases. This unusual condition, sometimes referred to as marantic endocarditis, is occasionally associated with malignant neoplasms. The exact cause of the lesions is not clear, but some investigators have suggested that substances liberated by the neoplasm may be the cause of the endocardial damage. These lesions are considered to be fertile ground for the development of bacterial endocarditis. Another indirect effect of neoplasm on the heart has been described in patients with malignant carcinoid of the small intestine.[9] This remarkable syndrome consists of malignant carcinoid of the small intestine with metastasis to the liver and to other intra-abdominal organs, pulmonary stenosis, right-heart failure, bronchial asthma, and episodes of skin flushing which are followed by patchy cyanosis. The cause of the pulmonary stenosis is not known, but the investigators believe it is related to the carcinoid for apparently serotonin is liberated by the tumor and produces many of the unusual symptoms. This substance can be found in the peripheral blood, and its degradation products can be found in the urine.

Myxomas make up 50 per cent of the primary tumors of the heart. In 75 per cent of the cases the tumor is located in the left atrium. The tumor usually arises from the atrial septum near the fossa ovalis and is frequently attached by a stalk.[10] Primary fibroma of the valves, especially of the tricuspid, also occurs. Primary sarcomas occur most frequently in the right atrium and right ventricle. Various types of primary sarcomas have been reported to occur in the endocardial region and these include myxosarcoma, fibrosarcoma, endothelial sarcoma, and hemangoendothelial sarcoma.

Because of the location of these tumors, especially myxomas, cardiac embarrassment occurs, because of obstruction to the mitral valve, pulmonary veins, tricuspid valve, superior vena cava and inferior vena cava. The obstruction of these passageways may develop slowly and produce chronic symptoms, or the obstruction can develop suddenly, in the case of a pedunculated tumor, and symptoms can occur acutely.[11-12]

Obstruction of the mitral valve due to a tumor may simulate mitral stenosis due to rheumatic heart disease.[13] When obstruction occurs slowly, chronic congestive heart failure may result with dyspnea on effort, paroxysmal nocturnal dyspnea, fatigue, auricular fibrillation, and peripheral emboli. This may be followed by edema, hepatomegaly, ascites, and increased venous pressure. If the obstruction occurs intermittently, due to a pedunculated tumor, the symptoms of a ball-valve blockade occur. The patient may experience syncope when he stands, "epileptiform fits," coma, shock, and gangrene of the nose and toes. Patients have been known to die of acute pulmonary edema in such cases, and under such circumstances the clinical picture simulates the "acute pulmonary edema" that occurs secondary to mitral stenosis due to rheumatic heart disease. A left atrial tumor may produce a diastolic rumble and a systolic murmur at the apex that are similar to the murmurs of rheumatic mitral valve disease. The murmurs vary from time to time when due to tumor and may be altered in an unexpected manner when the position of the patient is changed.

Several syndromes may be the result of right atrial tumors.[14] A condition may result which superficially simulates constrictive pericarditis with increased venous pressure, hepatomegaly, ascites, and edema. Under such circumstances the ventricular pulsations are usually normal, thereby differentiating the syndrome from constrictive pericarditis. A tricuspid diastolic rumble may be heard at the lower end of the sternum due to the tumor obstructing the tricuspid orifice with this murmur varying in intensity from time to time. In the absence of rheumatic mitral and aortic valve disease, the findings of tricuspid stenosis should suggest right atrial tumor. Peripheral gangrene of the nose tip and toes can be produced by the tricuspid blockade of a right atrial ball-valve tumor, but usually such symptoms are due to mitral valve obstruction.[15] Occasionally, the superior vena cava is obstructed more than the inferior, and a superior vena caval syndrome may result.[16] This syndrome is characterized by edema and cyanosis of the face, distended neck veins, and dilated veins of the chest wall. Pulmonary emboli may be the result of dislodged thrombi which have formed on a necrotic right atrial tumor. Various cardiac arrhythmias may occur in cases of left or right atrial tumor with sudden death occurring in one-third of the cases. Routine x-rays are occasionally helpful in establishing the diagnosis of right atrial tumor, but the diagnosis is usually made angiocardiographically.[17] Angiocardiography is indicated when there is an unusual clinical picture of constrictive pericarditis, the findings of tricuspid stenosis without aortic or mitral valve disease, and when there is an unexplained superior vena caval syndrome especially when a routine film shows an "irregular and lobular" cardiac outline. Tumors within the cardiac chambers have been attacked surgically. Experience in this regard is limited, but sufficient evidence has accumulated to indicate such treatment is within the range of possibility.

2. *Neoplastic involvement of the myocardial region:* Cardiac enlargement and congestive heart failure may occur indicating extensive, diffuse, metastatic neoplastic involvement of the myocardium.[18,19] A ventricular gallop may be the earliest sign of myocardial weakness, and typical congestive symptoms,

including pulmonary and peripheral edema, are not unusual. Because of the nature of the disease, the congestive heart failure is usually progressive and resistant to therapy. X-ray therapy may occasionally be of transient benefit.

Case 1, a patient with reticulum cell sarcoma, developed severe progressive congestive heart failure and, as predicted before death, proved to have extensive neoplastic involvement of the myocardium and pericardium. Bronchial breathing was heard over the lower sternum. This sign may indicate neoplastic involvement of the anterior mediastinum, including the heart and pericardium, from the trachea and bronchi to the sternum.

When there are only a few small localized metastatic lesions in the myocardium, few symptoms and signs result. Such lesions may produce arrhythmias and various electrocardiographic abnormalities which are discussed under separate headings.

A primary lipoma or a primary fibroma may occur as a large mass in the ventricular muscle or septum with resulting symptoms due to compression. Classical congestive heart failure is rare in such cases. A more common myocardial tumor is the rhabdomyoma. There is still much confusion among pathologists regarding the true nature of the rhabdomyoma.[20] The true rhabdomyoma is usually associated with tuberous sclerosis of the brain, adenoma sebaceum of the skin, and multiple tumors of the kidney. There is a delay in walking and in mental development. Various arrhythmias occur and convulsions may be due to tuberous sclerosis or Stokes-Adams attacks. Death occurs at an early age. Rhabdomyomas are said to be hamartomas and represent an arrest in maturation of cardiac muscle. These tumors do not grow, and the rarer rhabdomyosarcoma does not arise from them. "Hamartomas" composed of fat, fibrous tissue, muscle, blood vessels, and nerves have also been reported to originate in the myocardium. The diffuse "rhabdomyomas" are probably examples of glycogen storage disease. A myocardial tumor may invade the pericardium and produce pericarditis with bloody pericardial fluid.

Occasionally metastatic neoplastic lesions may involve the atrioventricular conduction system, and the various grades of heart block, including complete heart block, may result. Cases with primary cardiac hemangiomas and lymphangiomas have been reported. Many of these "tumors" have been located in or near the interatrial or interventricular septum adjacent to the A-V conduction system and produce complete heart block, Stokes-Adams attacks, and death. The tumors may be benign and resemble the cases of "cardiac varices." However, many are grouped under the sarcomas as hemangiosarcoma or lymphangiosarcoma. Other tumors including fibroma, lipoma, myxoma, rhabdomyoma, etc., can also damage the conduction pathway. It would be difficult to establish the diagnosis of cardiac neoplasm in such cases unless other signs of tumor were identified.

3. *Neoplastic involvement of the pericardium:* Neoplastic involvement of the pericardium must always be considered when the symptoms, signs, and electrocardiographic abnormalities of *acute pericarditis* make their appearance in a patient with known malignancy. Under such circumstances, the statistical

chance of the pericarditis being related to the neoplasm is great. It must be pointed out, however, that the pericarditis associated with extracardiac malignancy is not always due to actual neoplastic involvement of the pericardium with metastatic lesions. Some patients dying of malignant disease may have symptoms of acute pericardial disease, and no metastatic lesions may be found in the pericardium at autopsy to account for the pericarditis. Accordingly, the clinical picture of persistent fibrinous pericarditis is suggestive but not diagnostic of pericardial metastatic lesions.

Pericarditis due to metastatic disease may occur rarely when there is no evidence of the primary malignancy and one is forced to consider all causes of pericarditis.[21] In clinical practice one is likely to encounter rheumatic pericarditis, acute nonspecific pericarditis, tuberculous pericarditis, uremic pericarditis, pericarditis secondary to myocardial infarction, pyogenic pericarditis, and traumatic pericarditis and is less likely to encounter pericarditis due to neoplasm and lupus erythematosus.

Rheumatic pericarditis is usually associated with other signs of acute rheumatic fever. Evidence of myocarditis is common and cardiac murmurs frequently precede or appear during the course of the illness.

Acute nonspecific pericarditis is a self-limiting disease that frequently occurs abruptly a week or more after an upper respiratory tract infection. Precordial or substernal pain with or without radiation to the neck and arms is the prominent feature of the disease. The pain is characteristically aggravated by breathing, swallowing, and body motion from the onset. Fever, chills, and malaise are common and are frequently noted by the patient. These symptoms may precede the chest pain or occur shortly after the pain begins. A pericardial friction rub is frequently heard during the first day and may persist for one to two weeks. Cases have been reported where the friction rub persisted for 2 months, but this is exceptional. The white blood cell count is usually elevated and the sedimentation rate is accelerated early in the course of the disease. A ventricular gallop rhythm is heard on rare occasions, and some clinicians have indicated their belief that there is associated reversible myocarditis. Pericardial effusion may be present, but it is seldom necessary to aspirate the fluid except for diagnostic reasons. As discussed later, hemorrhagic fluid has been reported in this disease. The prognosis of acute benign pericarditis is good although recurrences are not uncommon. As a rule definite clinical improvement occurs within one week, and most patients are well within six weeks.

Acute benign pericarditis is frequently misdiagnosed as myocardial infarction. The number of mistakes is decreased if one recalls that the pain of acute benign pericarditis is aggravated by breathing at the onset while the pain of myocardial infarct is constant. The pericarditis associated with myocardial infarction is aggravated by breathing, but this complication of the infarct occurs 36 to 48 hours after the original chest pain. Likewise the friction rub, leukocytosis, fever, and accelerated sedimentation rate occur approximately two days after the infarction. The electrocardiogram shows ST-T changes in benign pericarditis, and the characteristic QRS changes of infarct do not develop.

Hemorrhagic pericardial effusion can occur as a complication of myocardial infarct and is discussed later.

Tuberculous pericarditis is not difficult to diagnose in patients with known pulmonary tuberculosis, but the etiology may be difficult to establish when there is no evidence of the disease elsewhere. The disease usually begins insidiously and is associated with fever, malaise, and sweats. The pain of tuberculous pericarditis is usually mild, but experience with several cases has taught us that the pain may occasionally be severe. A pericardial friction rub is frequently heard. If the friction rub persists for weeks or if considerable pericardial fluid accumulates, then one should strongly suspect a tuberculous etiology. The white blood count may be normal, low, or slightly elevated. The characteristics of tuberculous pericardial effusion are discussed later. The skin test for tuberculosis must always be done in patients with pericarditis of unknown origin. If the tuberculin skin test is negative, one can exclude a tuberculous origin for pericarditis. However, there are a few exceptions to this rule especially in the last days of a debilitating illness.

Uremic pericarditis occurs during the terminal phase of uremia and is usually recognized by identifying a loud pericardial friction rub which may last for a considerable period and may not be associated with pain. The characteristic electrocardiographic abnormalities of pericarditis may not occur.

Pyogenic pericarditis is usually a complication of pyogenic infection elsewhere in the body. Most cases occur during the course of pneumonia, bacterial endocarditis, meningococcemia, and osteomyelitis. Septic pericarditis is usually recognized by either hearing a pericardial friction rub or finding evidence of pericardial effusion during the course of a septic disease. The electrocardiographic evidence of pericarditis is usually present. When the clinical and x-ray evidence of pericardial effusion is present, then a pericardial aspiration is indicated. The fluid shows many polymorphonuclear leukocytes; smear and culture may reveal the causitive organism.

Traumatic pericarditis may follow penetrating and nonpentrating wounds of the chest or follow surgical procedures requiring incision of the pericardium. The diagnosis is usually made when a friction rub is heard, or when pericardial effusion occurs after an injury.

Pericarditis in lupus erythrematosis has been recognized on several occasions during the last several years. When the clinical picture of pericarditis is present and the cause is not known, then the blood should be studied for the abnormal cells of lupus. Other procedures, useful in identifying the "collagenous" diseases, should also be carried out.

As a rule, no great difficulty should be encountered in making the diagnosis of rheumatic pericarditis, acute benign pericarditis, the pericarditis of myocardial infarction, pyogenic pericarditis, and traumatic pericarditis. Considerable difficulty may be found in establishing the etiology of the pericarditis when it is due either to tuberculosis, neoplastic disease, or to collagenous tissue disease. These causes should be suspected when the course of the disease is prolonged, and there are none of the common causes of pericarditis. A careful search must be carried out for evidence of tuberculosis, neoplasm, and "collagenous" tissue

disease elsewhere in the body. The diagnosis can frequently be made by studying the pericardial fluid of such cases. If there is insufficient fluid to be studied or if a diagnosis cannot be established after studying the fluid, then a pericardial biopsy is indicated. If pericardial fluid and a pericardial biopsy reveal no clue as to the diagnosis, then antituberculous therapy may be justified in a tuberculin-positive person with persistent evidence of pericarditis.

In Case 1, a patient with reticulum cell sarcoma, pericarditis was the first clue to neoplastic involvement of the heart.

Metastatic neoplastic disease of the heart and pericardium must always be considered when *pericardial effusion* becomes apparent in patients with malignancy elsewhere. If the primary neoplasm has not been recognized, then the etiologic diagnosis becomes more difficult. It is useful to recall the clinical characteristics of the following conditions. Pericardial effusion secondary to rheumatic pericarditis is not difficult to diagnose in most cases since there is usually preceding or subsequent collateral evidence of rheumatic fever and myocarditis. Therapeutic pericardial aspiration is seldom necessary. Uremic pericarditis is easily recognized and seldom requires aspiration for treatment or recognition. Hemopericardium results from trauma, rupture of myocardial infarction, or dissecting aortic aneurysm and, in such cases, the etiology is easily established. Idiopathic pericarditis may rarely be associated with sufficient pericardial effusion to necessitate aspiration. It has recently been pointed out that the pericardial fluid in such cases may be hemorrhagic. Patients with myxedema and beriberi may develop hydropericardium, but the etiology is usually apparent and therapeutic aspiration is not required. An important complication of myocardial infarction is hemorrhagic effusion. This is not to be confused with myocardial rupture which leads to hemopericardium. The symptoms and signs of hemorrhagic effusion have occurred more often in patients who are on anticoagulants but have occurred in patients not receiving such therapy. This complication may occur one to two weeks after a myocardial infarct and is characterized by high temperature, leukocytosis, dyspnea, anterior chest pain aggravated by breathing, and pulsus paradoxus.

Tuberculous pericarditis and neoplastic involvement of the heart and pericardium are the most common nontraumatic causes of cardiac tamponade. Williams and Souter have emphasized how frequently cardiac tamponade is overlooked and have pointed out the misconceptions regarding the signs of massive effusion.[22] Unfortunately many cases of cardiac tamponade are not diagnosed because no search has been made for a pulsus paradoxus and the neck veins have not been studied properly. In addition, the diagnosis may not be considered if the heart sounds are normal or if there is a pericardial friction rub since it has been taught erroneously in the past that the heart sounds and friction rub always decrease in intensity when there is pericardial fluid. The cardiac silhouette is usually enlarged, and the pulsations are usually noted to be decreased when the heart is examined fluoroscopically. However, this is not diagnostic since diffuse cardiac enlargement may give a similar finding. Pericardial fluid may produce "smoothing out" of the cardiac contours, cause the root of the aorta and pulmonary artery to be short and broad, prevent the

cardiac silhouette from decreasing during the Valsalva maneuver, and cause the heart shadow to increase in size when the patient lies down. Although such signs are helpful they are, in reality, rather poor signs and numerous cases are encountered when one cannot distinguish between generalized enlargement and pericardial effusion. The following clues are perhaps more helpful. (1) When the cardiac shadow increases greatly in size within a few days and the lung fields remain clear, then pericardial effusion is likely. (2) When the heart shadow is large, the pulsation greatly decreases, and the lung fields are clear, then pericardial effusion is likely. The electrocardiogram usually shows decreased voltage and ST-T abnormality, but this can occur with diffuse myocardial disease. At times one is justified in performing an angiocardiogram when the differential diagnosis lies between pericardial effusion and diffuse myocardial disease. Pericardial aspiration may be done for diagnosis and for the relief of severe tamponade. The pericardial fluid is usually hemorrhagic when due to neoplasm or tuberculosis and tends to reaccumulate rapidly. The total eosinophil count of the peripheral blood in patients with hemorrhagic pericardial effusion is more likely to be elevated when due to neoplasm than when due to tuberculosis.[23] The pericardial fluid must be studied for malignant cells and must be cultured for *tubercle bacilli* in addition to the routine examination. A word of caution must be interjected here since certain cells in pericardial fluid may resemble malignant cells and even expert pathologists may be led astray. A simple hemoglobin determination on the pericardial fluid must never be omitted since errors are sometimes made when it is assumed that the bloody fluid resulted from a ventricular puncture. When the pericardial fluid does not reveal the etiology, then one is justified in performing a pericardial biopsy for diagnostic purposes. If the fluid has had the tendency to reaccumulate rapidly after repeated aspirations, then a pleuropericardial window or pericardial resection is considered the treatment of choice since the use of radioactive gold or chrome phosphate is usually of little value. The biopsy or the pericardial sac can be studied for neoplasm and tuberculosis as well as other diseases. A word of caution must also be interjected here. We have seen cases of pericarditis and pericardial effusion due to neoplasm yield negative pericardial biopsies and pericardial sections. It is also interesting to note that some patients who have had a tendency to accumulate a large amount of hemorrhagic fluid rapidly may exhibit relatively few metastatic lesions in the pericardium at autopsy. It appears that the entire pericardium "weeps" fluid.

When no diagnosis can be established in a tuberculin-positive individual with persistent pericardial effusion, antituberculous therapy is frequently justified.

Case 2, a patient with bronchogenic carcinoma, developed massive hemorrhagic pericardial effusion as the initial problem. As is characteristic of effusions due to neoplasm, the fluid reaccumulated rapidly. Malignant cells were identified in the fluid. The instillation of radioactive chrome phosphate into the pericardial sac was not helpful.

Constrictive pericarditis is often secondary to chronic tuberculous pericarditis but many cases are the result of pericardial scarring of unknown origin. Some

cases are due to pericardial or heart trauma while others are secondary to healed infectious pericarditis due to a variety of organisms. Constrictive pericarditis can also be caused by metastatic neoplastic involvement of the pericardium.[24,25] Whenever the signs and symptoms of constrictive pericarditis occur in a patient with known malignancy, one should suspect neoplastic involvement of the pericardium and heart. This is particularly likely to be the cause when the primary neoplasm originates in the breast or bronchus. When the primary site of the neoplasm cannot be recognized, and there are no metastatic lesions elsewhere, then one can only add metastatic disease to the list of possible causes. The etiology in such cases can only be determined by pericardial biopsy or examination of the resected pericardium.

Secondary neoplastic involvement of the pericardium without evidence of a primary source is probably more common than is primary pericardial neoplasm. The two conditions give similar clinical pictures and cannot be separated with certainty on every occasion. Primary neoplasms of the pericardium include lipoma, fibroma, sarcoma (all types), mesothelioma, teratoma, hemangioma, dermoids, and hamartomas.[26-30] These tumors may produce acute and persistent pericarditis, hemorrhagic pericardial effusion and cardiac tamponade, and constrictive pericarditis. The nature of the disease is occasionally discovered by studying the pericardial fluid or by obtaining a pericardial biopsy. Pericardial resection is the treatment of choice for recurrent hemorrhagic effusion due to primary neoplasm of the pericardium and for constrictive pericarditis if the symptoms justify the surgery.

4. *Cardiac arrhythmias:* Cardiac arrhythmias are nonspecific and occur with and without demonstrable evidence of cardiac disease. All types of arrhythmias have been reported to occur in patients with primary and secondary neoplastic disease of the heart, and the list includes paroxysmal auricular tachycardia, auricular fibrillation and flutter, ventricular tachycardia, and various grades of atrioventricular block including complete heart block.

A few of the sudden and unexpected deaths that occur in patients with neoplasm are undoubtedly due to cardiac arrhythmias. Cardiac arrhythmias occur when the metastatic lesions involve the atria or ventricles of the heart. Since cardiac arrhythmias are nonspecific, their appearance in patients with malignancy cannot be considered to be conclusive evidence of metastatic cardiac involvement.[19] The various atrioventricular conduction defects are more diagnostic of neoplastic involvement of the heart then are other types of arrhythmias. For example, 2:1 atrioventricular block in a 30-year-old woman dying of leukemia is more suggestive of cardiac infiltration than is paroxysmal auricular tachycardia.

Case 1, a patient with reticulum cell sarcoma, exhibited paroxysmal auricular fibrillation. Although the diagnosis could have been established even if the arrhythmia had not occurred, it was this abnormality which prompted a detailed evaluation of the patient's cardiac status. Case 3, a patient with neuroblastoma of the pericardium, experienced episodes of paroxysmal nodal tachycardia.

5. *Electrocardiographic abnormalities:* Nonspecific electrocardiographic

abnormalities are common in patients with neoplastic disease of the heart and pericardium.[6] The various arrhythmias already listed may be recorded by the electrocardiograph. The P waves may be large and bizarre as a result of atrial involvement. The ST-T abnormalities due to pericarditis may occur. Low voltage secondary to pericardial effusion or to diffuse myocardial replacement by neoplasm may be observed. The various grades of atrioventricular block and right and left bundle branch block secondary to neoplastic involvement of the conduction system have been reported. The electrocardiogram, on rare occasions, may simulate an ordinary myocardial infarction including an abnormality of the initial portion of the QRS complex. Nonspecific T-wave abnormality is the most common electrocardiographic finding in patients with cardiac metastasis. The finding of an electrocardiographic abnormality in a patient dying of malignancy may or may not be related to the neoplastic process. If the more common causes of electrocardiographic abnormalities can be eliminated, then even nonspecific deviations from the normal should force one to search carefully for more diagnostic clues. For example, low voltage in the electrocardiogram would force one to carefully evaluate the patient for pericardial effusion.

Case 1, a patient with reticulum cell sarcoma, revealed electrocardiograhic signs of pericarditis, then auricular fibrillation, and finally there was suggestive electrocardiographic evidence of an anterior myocardial infarction. Case 2, a patient with bronchogenic carcinoma with metastasis to the heart, showed low voltage in the electrocardiogram due to pericardial effusion. Case 3, a patient with neuroblastoma of the pericardium, showed electrocardiographic evidence of pericarditis.

6. *Routine x-ray examination of the heart and angiocardiography:* Although x-ray examination of the heart is usually normal in patients with metastatic malignant disease of the heart and pericardium the following abnormalities are commonly encountered. Progressive enlargement of the cardiac silhouette in a patient with neoplasm elsewhere in the body may indicate either diffuse myocardial disease with cardiac enlargement or pericardial effusion. The problem of differentiating these two conditions has been discussed under pericardial effusion. Occasionally the cardiac contour may become irregular and show a nodular outline because of tumor masses.

Angiocardiography is sometimes indispensable in the study of the disease under discussion. Angiocardiography is indicated when (a) the cardiac contour is unusual or irregular; (b) certain shadows adjacent to the heart cannot be properly delineated; (c) one is unable to differentiate between generalized cardiac enlargement and pericardial effusion; (d) the signs and symptoms of mitral stenosis are atypical, when the left atrium has an irregular outline, or when there is evidence of a ball-valve blockade; (e) there is evidence of tricuspid stenosis without evidence of mitral or aortic valve disease; (f) the superior vena caval syndrome is present without demonstrable cause; (g) the signs of constrictive pericarditis are present and ventricular pulsations are normal, or when there is a suggestive mass adjacent to the heart (h) there are repeated peripheral emboli without apparent cause.

One may be unable to determine by angiocardiography whether the tumor mass has its origin in the endocardium, myocardium, or pericardium but will be able to identify deformed, compressed, cardiac chambers. Then by correlating the angiocardiographic findings with the clinical findings, one may be able to determine if the mass arises inside the heart or if the heart is compressed from without (i.e., pericarditis is less common in cases of endocardial than with pericardial or myocardial tumor).

Case 1 exhibited an unusual lobulated contour in the region of the right ventricle. Case 2 had x-ray evidence of pericardial effusion. Case 3 had an unusual cardiac contour in the region of the left ventricle, and this area did not pulsate while the other regions pulsated vigorously. Case 3 also demonstrated the value of angiocardiography by showing a large tumor mass compressing the cardiac chambers.

SUMMARY

1. Neoplastic disease of the heart is seldom recognized even though it is no longer considered unusual.

2. Cardiac lesions are found at autopsy in 20 per cent of the patients dying of malignancy. This type of disease usually causes no cardiac signs and symptoms but can be diagnosed clinically in about 5 to 10 per cent of such patients.

3. Primary neoplasms of the heart and pericardium are exceedingly rare but must be considered in the differential diagnosis of unusual heart disease.

4. From a clinical standpoint, one can think in terms of (1) a clinical picture due to neoplastic involvement of the endocardial region, (2) a clinical picture due to neoplastic involvement of the myocardium, (3) a clinical picture due to neoplastic involvement of the pericardium. Such a classification is not intended to imply that the new growth actually originates in the region which produces the symptoms and signs.

5. Endocardial implants of neoplastic metastatic tissue seldom produce symptoms or signs of heart disease. Degenerative verrucal endocardial lesions are occasionally related to a malignant neoplasm and are considered fertile ground for the development of bacterial endocarditis. The curious syndrome of carcinoid of the small intestine and pulmonary stenosis is mentioned. Myxomas make up 50 per cent of the primary tumors of the heart and 75 per cent of such tumors as are located in the left atrium. Symptoms occur because of obstruction to the mitral valve, pulmonary veins, tricuspid valve, and superior and inferior vena cava. The patient's symptoms and signs may simulate rheumatic mitral stenosis, ball-valve blockade of the mitral or tricuspid valve, rheumatic tricuspid stenosis, and constrictive pericarditis. Clues that are useful in suspecting the true nature of the disease are pointed out.

6. Extensive metastatic neoplastic involvement of the myocardium may produce congestive heart failure. One should consider this type of disease when a patient with known malignancy develops congestive heart failure without obvious cause. The physical finding of bronchial breathing over the sternum may indicate anterior mediastinal neoplastic involvement, including the heart

and pericardium, from the trachea and bronchi to the sternum. Small lesions in the myocardium produce arrhythmias and various electrocardiographic abnormalities. The most common primary myocardial tumor is the rhabdomyoma, and this tumor is frequently associated with tuberous sclerosis of the brain and adenoma sebaceum of the skin. Primary and secondary neoplastic involvement of the heart may involve the conduction system of the heart and produce the various grades of heart block.

7. Neoplastic involvement of the pericardium must always be considered when the symptoms, signs, and electrocardiographic abnormalities characteristic of pericardial disease make their appearance in a patient with a malignancy. Acute pericarditis, pericardial effusion, and constrictive pericarditis can be the result of primary and secondary neoplasms. Certain diagnostic clues are pointed out in a brief discussion of the various types of pericardial disease.

8. All types of cardiac arrhythmias have been reported to occur in cases of primary and secondary neoplastic disease of the heart. High grades of atrioventricular conduction defects are more diagnostic of cardiac involvement than are other arrhythmias in younger patients with known malignancy.

9. Nonspecific electrocardiographic abnormalities are common in patients with neoplastic disease of the heart. Nonspecific T-wave abnormalities, bizarre P waves, evidence of pericarditis or pericardial effusion, and the QRS abnormalities of "dead zone" have all been reported in addition to the various cardiac arrhythmias.

10. The x-ray findings of neoplastic disease of the heart have been listed, and several indications for angiocardiography have been emphasized.

11. It is hoped that some intracavitary cardiac tumors can be removed (i.e., myxoma of the left atrium). X-ray therapy may offer transient benefit for neoplastic involvement of the myocardium and pericardium when the tissue is radiosensitive. The surgical production of a pleuropericardial window or pericardial resection is considered the treatment of choice for massive hemorrhagic pericardial effusion that reaccumulates rapidly.

ADDENDUM

After this review was completed, Goldberg and Steinberg published an excellent article on "Primary Tumors of the Heart" (Circulation 11:963, 1955) They had received a communication from Crafoord indicating that he had successfully removed a pseudomyxoma of the left atrium in a patient who had symptoms of paroxysmal mitral valve occlusion.

REFERENCES

1. Summers, D.: The Metastasis of Tumors, Am. J. M. Sc. **145**:225, 1917.
2. Burke, E. M.: Metastatic Tumors of the Heart, Am. J. Cancer **20**:33, 1934.
3. Pollia, J. A., and Godal, L. J.: Some Notes on Malignancies of the Heart, Am. J. Cancer **27**:329, 1936.
4. Burnett, R. C., and Shimkin, B.: Secondary Neoplasms of the Heart, Arch. Int. Med. **93**:205, 1954.
5. Young, J. M., and Goldman, R. D.: Tumor Metastasis of the Heart, Circulation **9**:220, 1954.
6. Bisel, H. F., Wroblewski, F., and Ladue, J. S.: Incidence and Clinical Manifestations of Cardiac Metastases, J.A.M.A. **153**:712, 1953.
7. Willis, R. A.: The Spread of Tumors in the Human Body, St. Louis, 1952, The C. V. Mosby Company.

8. Allen, A. C., and Sirota, J. H.: The Morphogenesis and Significance of Degenerative Verrucal Endocardiosis (Terminal Endocarditis, Endocarditis Simplex, Nonbacterial Thrombotic Endocarditis), Am. J. Path. **20**:1025, 1944.
9. Thorson, A., Biörck, G., Björkman, G., and Waldenström, J.: Malignant Carcinoid of the Small Intestines With Metastases to the Liver, Valvular Disease of the Right Side of the Heart (Pulmonary Stenosis and Tricuspid Regurgitation Without Septal Defects) Peripheral Vasomotor Symptoms, Bronchoconstriction and an Unusual Type of Cyanosis, Am. Heart J. **47**:795, 1954.
10. Friedberg, C.: Diseases of the Heart, 1949, W. B. Saunders Company, page 995.
11. Hughes, S. B., and Fazlullah, S.: Cardiac Failure Due to Tumor of the Left Atrium, Brit. Heart J. **16**:326, 1954.
12. Madonia, P. F., Baggiano, R., and Gubner, R.: Ball-Valve Syndrome Caused by Primary Cardiac Tumors, New York J. Med. **53**:3043, 1953.
13. Harrison, J. W., McCormack, L. J., and Ernstene, A. C.: Myxoma of the Left Atrium Simulating Mitral Stenosis, Circulation **10**:766, 1954.
14. Bahnson, H. T., and Newman, E. V.: Diagnosis and Surgical Removal of Intra-Cavitary Myxoma of the Right Atrium, Bull. Johns Hopkins Hosp. **93**:150, 1953.
15. Kendall, D., and Symonds, B.: Epileptiform Attacks Due to Myxoma of the Right Auricle, Brit. Heart J. **14**:139, 1952.
16. Weller, G. L.: Clinical Aspects of Cardiac Involvement (Right Auricular Tumor) in Idiopathic Hemorrhagic Sarcoma (Kaposis Disease), Ann. Int. Med. **14**:314, 1940.
17. Steinberg, I., Dotter, C. T., and Glen, F.: Myxoma of the Heart, Roentgen Diagnosis During Life in Three Cases, Dis. Chest **24**:509, 1953.
18. Yater, W. M.: Tumors of the Heart and Pericardium, Arch. Int. Med. **48**:627, 1931.
19. Scott, R. W., and Garvin, G. F.: Tumors of the Heart and Pericardium, Am. Heart J. **17**:431, 1939.
20. Farber, S.: Congenital Rhabdomyoma of the Heart, Am. J. Path. **7**:105, 1931.
21. McQuire, J., Kotte, J. H., and Helm, R.: Acute Pericarditis, Circulation **9**:425, 1954.
22. Williams, C., and Souter, L.: Pericardial Tamponade, A.M.A. Arch. Int. Med. **94**:571, 1954.
23. Jaegers, H.: Personal communication.
24. Slater, S. R., Kroop, I. G., and Zukerman, S.: Constrictive Pericarditis Caused by Solitary Metastatic Carcinosis of the Pericardium and Complicated by Radiation Fibrosis of the Mediastinum, Am. Heart J. **43**:401, 1952.
25. Wallace, J. J., and Logue, R. B.: Metastatic Carcinoma as a Cause of Constrictive Pericarditis, Am. Heart J. **31**:223, 1946.
26. Solomon, R. D.: Malignant Teratoma of the Heart, Arch. Int. Med. **52**:561, 1951.
27. Hochberg, L. A., and Robinson, A. I.: Primary Tumors of the Pericardium Involving the Myocardium, Surgical Removal, Circulation **1**:805, 1950.
28. Beirne, M. F., Berkheiser, S., and Roderick, C.: Intra-Pericardial Dermoid Cyst, Am. J. Surg. **87**:924, 1954.
29. Dowe, C. J., Wood, D. A., and Mitchell, S.: Diffuse Mesothelioma of the Pericardium, Cancer **6**:794, 1953.
30. Fisher, E. R., Bollinger, C. S., and Effler, D. B.: Hamartoma of the Pericardium—Lymphatic Type, Cleveland Clin. Quart. **18**:12, 1951.

Book Review

Cardiac Auscultation; Including Audio-visual Principles. By J. Scott Butterworth, M.D., Maurice R. Chassin, M.D., and Robert McGrath, M.D., New York and London, 1955, Grune & Stratton, Inc., 111 pages.

This volume contains a short and lucid description of the important, more common auscultatory findings in the heart. In the early chapters the physical principles of acoustics are taken up and then some general remarks about the value of auscultation. There follows a discussion of the arrhythmias and finally the detection and interpretation of heart murmurs. This book is clearly illustrated by numerous figures, fifty-four in all. The reproductions of the heart sounds and murmurs are quite clear. The various cardiac murmurs are graphically displayed in these stethograms.

The general purpose of such a book is to teach auscultation of the heart and in that way make it less necessary to have graphic records for diagnostic purposes. It can be highly recommended to any physician or internist as an aid in the practice of auscultation of the heart.

S. A. L.

Erratum

In the article by Gross, Kepes, Young, and Enselberg entitled "Electrocardiographic Changes During Mitral Commissurotomy" which appeared in the September issue of the Journal, pages 373-381, the following changes should be made in the illustrations: Fig. 1 should be reversed as to top and bottom; the cuts for Figs. 2 and 4 should be transposed, leaving the legends in their present position.

Announcements

A course in INTERPRETATION OF COMPLEX ARRHYTHMIAS will be given at Michael Reese Hospital by Louis N. Katz, M.D., Richard Langendorf, M.D., and Alfred Pick, M.D. This is an *advanced* course intended only for experienced electrocardiographers. The class will meet daily from 9:00 A.M. to 5:00 P.M., Dec. 5-9, 1955.

Further information and a copy of the lecture schedule may be obtained from the Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Illinois.

A five-day program on FLUID AND ELECTROLYTE BALANCE, under the chairmanship of Dr. George E. Burch, Professor of Internal Medicine, will be presented Jan. 16-21, 1956, through the Division of Graduate Medicine of Tulane University School of Medicine.

The course is planned as a review of the fundamental principles of water and electrolyte metabolism, but will also emphasize the clinical applications of these principles. Frequent conferences and discussions at the bedside of patients will be held. Inquiries may be addressed to the Director, Division of Graduate Medicine, 1430 Tulane Avenue, New Orleans 12, Louisiana.

The SECOND EUROPEAN CONGRESS OF CARDIOLOGY will take place in Stockholm, Sweden, Sept. 10 to 14, 1956. The European Society of Cardiology, which arranges the European Congresses of Cardiology, has entrusted the Swedish Society of Cardiology with organizing this Congress. The site of the scientific sessions and the exhibitions will be the Concert Hall.

The preliminary program for panel discussions and round-table conferences has been made up as follows:

Panel Discussions.—

1. Etiology and Pathogenesis of Atherosclerosis.
2. Isolated Atrial and Ventricular Septal Defects.
3. Pulmonary Hypertension.
4. Cardiac Output and Its Regulation.
5. Acquired Aortic Stenosis.
6. Circulation in Hypothermia.
7. Organic Peripheral Arterial Disease.

Round-Table Conferences.—

1. Treatment of Essential Hypertension.
2. Treatment of Paroxysmal Arrhythmias and Other Ectopic Rhythms.
3. Phonocardiography.
4. Indications and Hazards of Heart Catheterization and Angiocardiography.

Another item to be discussed will be: The Applicability of the Roentgenological Heart Volume Determination.

The Congress will be open in the first place to members of the National Heart Societies affiliated to the European Society of Cardiology. As far as space allows, it will be open also to other doctors interested in cardiology both within and outside Europe.

The address of the Congress is: Södersjukhuset, Stockholm S., Sweden.